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# Subclinical Atherosclerosis in Children with Rheumatologic Diseases in Minia Children University Hospital, Egypt

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***Abstract***

***Background:*** Patients with rheumatologic diseases have higher rates of cardiovascular disease. Accelerated atherosclerosis and early coronary artery disease have become important causes of death and hospitalization in those patients which may be attributed to metabolic changes in lipids. We aimed to clarify the cardiovascular risk in children with juvenile idiopathic arthritis (JRA), and systemic lupus erythematosus (SLE), and its relation to lipid profile and disease activity index.

***Materials and Methods***

In this cross sectional comparative study which was done in Minia Children University Hospital, Egypt, we measured lipid profile (cholesterol, triglycerides, low and high density lipoproteins), erythrocyte sedimentation rate, and C-reactive protein in 15 patients with JRA (group1), and 15 patients with SLE (group 2), and in 30 healthy children as controls (group 3).

***Results***

Results showed that there were no significant differences between group 1 (JRA) patients, and controls in total cholesterol, triglycerides, low and high density lipoproteins, but there were high statistically significant differences between group 2 (SLE) patients, and controls in total cholesterol, triglycerides, low density lipoproteins ($p<0.001$), and in high density lipoproteins ($p<0.008$).There were positive significant correlations between disease activity index in JRA patients with total cholesterol ($r=0.633$, $p=0.011$), triglycerides ($r=0.523$, $p=0.046$), and low density lipoproteins ($r=0.548$, $p=0.034$). Also, positive significant correlations between disease activity index in SLE patients with total cholesterol ($r=0.579$, $p=0.024$), triglycerides ($r=0.559$, $p=0.030$), and low-density lipoprotein ($r=0.533$, $p=0.041$).

***Conclusion***

Children with rheumatologic diseases can be at high risk of arthrosclerosis and cardiovascular events due to lipid profile change which may be associated with subclinical arthrosclerosis, so continuous monitoring of lipid profile can decrease mortality and co-morbidity.

***Key Words:*** Arthrosclerosis, Children, Juvenile idiopathic arthritis, SLE.

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## 1- INTRODUCTION

Pediatric patients with juvenile idiopathic arthritis (JIA) have higher rates of morbidity and mortality than the general population, which is highly attributed to an increased risk of cardiovascular disease (CVD) among these patients (1, 2). The increased risk of CVD appears to be linked to coronary atherosclerosis (3, 4), and may be directly caused by chronic inflammation or secondarily caused by physical inactivity and drugs used to treat JIA (5). Accelerated atherosclerosis and early coronary artery disease have become important causes of death and hospitalization in systemic lupus erythematous (SLE) patients.

Lipid abnormalities may play a major role in increasing cardiovascular risk in SLE patients who are characterized by elevated triglycerides, very low-density lipoprotein cholesterol (VLDL-C), reduced levels of high-density lipoprotein cholesterol (HDL-C), and Apo lipoprotein (ApoA-1) (4). Endothelial injury is an important initial event in the development of atherosclerosis and therefore measurement of endothelial function can serve as a surrogate marker of atherosclerosis (3). We aimed to clarify the cardiovascular risk in children with juvenile idiopathic arthritis and systemic lupus erythematosus and its relation to lipid profile and disease activity index

## 2- MATERIALS AND METHODS

### 2-1. Method

The present study is a case control study conducted on 30 consecutive patients divided into15 children diagnosed as JIA (Group 1), and 15 children diagnosed as SLE (Group 2). They were selected from the attendants of the pediatric rheumatology and nephrology clinic in Minia University Children Hospital (Egypt), through the period from March 2017 to September 2017. Also, 30 apparently healthy volunteers who served as a control group (Group 3) of matched age and sex. Controls were selected from healthy children who came for regular follow- up in hospital outpatient clinic.

- JIA patients were diagnosed according to the International League of Associations for Rheumatology (ILAR) classification criteria, American College of Rheumatology (ACR) diagnostic criteria (2).
- SLE patients were diagnosed according to American College of Rheumatology (ACR) 1997, revised criteria for the classification of SLE (6).
- DAS28 was used for assessing disease activity in JIA patients. The DAS28 is an index similar to the original DAS, consisting of a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), ESR, and an optional general health assessment on a visual analogue scale (range 0-100) (7).
- Disease activity was assessed using the SLE Disease Activity Index (SLEDAI). The version covering the last 10 days was used. It is a validated disease activity measure that contains 24 descriptors in 9 organ systems, including clinical and laboratory measures of SLE activity, and is weighted to reflect the degree of activity. The total SLEDAI score can range from 0 (no activity) to 105 (maximum activity) as updated by Gladman et al. (2002). Activity categories have been defined on the basis of SLEDAI scores: no activity (SLEDAI: 0), mild activity (SLEDAI: 1-5), moderate activity (SLEDAI: 6-10), high activity (SLEDAI: 11-19), very high activity (SLEDAI $\geq$20) (8).

### 2-2. Laboratory investigations

Laboratory investigations included ESR, CRP and lipid profile (cholesterol, triglycerides, HDL and LDL).

#### 2-2-1. Blood samples

About 6 ml of venous blood were withdrawn from included children by sterile vein puncture after 12 h fasting. This sample was divided as follows:

- Two ml in sodium citrate solution for ESR.
- Four ml in two plain tubes: it was left to be clotted then centrifuged. Separated serum was used for determination of kidney function tests, liver enzymes and lipid profile.

### 2-3. The methods used

Total cholesterol and triglycerides were determined using fully automated clinical chemistry auto-analyzer system Konelab 20i (Thermo Electron Incorporation, Finland). Serum high density lipoprotein-cholesterol (HDL-c) was determined using Microlab 200 (Vital Scientific W-Holland) from kits supplied by Human Gesellschaft Fur Biochemical, and Diagnostic mbh, Germany (9). Serum low density lipoprotein- cholesterol (LDL-c) was calculated according to the equation as follows (9): LDL-c = TC – {(TGs/5) +HDL-c}, provided that triglyceride <400 mg%.

#### 2-3-1. Intima-media thickness (IMT)

IMT is measured as the distance between two echogenic lines, separated by echo lucent space in the wall of the artery. It is appropriate to measure thickness 3 times in the anterior, lateral and posterior plans (total of 18 measurements). Automated edge detector programs, instead of manual measurements, have made measurements faster and less variable. CIMT above the 75th percentile of average for the age, gender and ethnicity or absolute thickness more than 1.0 mm are considered an abnormal result, and people with IMT in less than the 50th percentile are classified in the low risk group (3). The 75th-percentile threshold is considered an abnormal result (10).

#### 2-3-2. Statistical method

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 20.0. Descriptive statistics were done for numerical data by mean, standard deviation and minimum and maximum of the range, while they were done for categorical data by number and percentage. Analyses were done for parametric quantitative variables using one way ANOVA test for comparison between three groups and post- hoc Tukey's correction between each two groups. Analyses were done for non-parametric quantitative variables using Kruskal Wallis test for comparison between three groups, and Mann Whitney test for comparison between each two groups. Analyses were done for quantitative variables using independent sample t- test for parametric data between the two groups. Chi- square test was used for qualitative data between groups. Correlation between two quantitative variables was done by using Pearson's correlation coefficient. Correlation coefficient ranges from (0-1): weak (r=0-0.24), fair (r=0.25-0.49), moderate (r=0.5-0.74), and strong (r=0.75-1). The level of significance was taken at (P- value $\leq 0.05$).

### 2-4. Ethics

The study followed the instructions of Research Ethics Committee in Faculty of Medicine, Minia University (Egypt). It was approved according to PN 34/15mu. An informed Arabic written consent to participate in our study was obtained from participants or their parent or legal guardian in the case of children under 16.0 years old.

## 3- RESULTS

Our study was carried out on 15 patients with JIA [5 males (33.3%), and 10 females (66.7%)], 15 patients with SLE [2 males (13.3%), and 13 females (86.7%)], and 30 healthy control children [14 males (46.7%), and 16 females (53.3%)]. **Table.1** shows disease markers including ESR (1st and 2nd h), and CRP were statistically significantly higher in JIA, SLE patients than controls. **Table.2** shows non-significant difference between group 1 and group 3 in TC, TG, LDL and HDL, but there were high statistically significant differences between group 2 and group 3 in TC , TG, LDL ($p<0.001$), and in HDL ($p<0.008$). **Table.3** shows significant positive correlations between DAI in group 1 with TC ($r=0.633$, $p=0.011$), TG ($r=0.523$, $p=0.046$), and LDL ($r=0.548$, $p=0.034$). Also, significant positive correlations between DAI in group 2 with TC ($r=0.579$, $p=0.024$), TG ($r=0.559$, $p=0.030$), and LDL ($r=0.533$, $p=0.041$). **Table.4** shows significant positive correlations between steroids doses with TC ($r=0.915$, $p=0.010$), LDL ($r=0.911$, $p=0.012$), and significant negative correlation between salazopyrin duration with HDL ($r=-1$, $p<0.001$), but no significant correlations between MTX duration and antimalarial drugs doses and durations. **Table.5** shows positive significant correlations between steroids durations with TC ($r=0.964$, $p<0.001$), LDL ($r=0.957$, $p<0.001$), and positive significant correlations between other treatments durations with TC ($r=0.688$, $p=0.007$), and LDL ($r=0.682$, $p=0.007$). **Table.6** shows a significantly higher IMT both in the left and in the right carotid artery compared to control children ($p<0.05$). The mean value of the left and the right carotid artery was significantly higher in study group compared with control ($p< 0.05$).

**Table-1**: Comparison between JIA, SLE as regards disease markers and disease activity.

| Marker, Mean ± SD | Group I (JIA), n=15 | Group II (SLE), n=15 | Group III (Control), n=30 | P- value |
|---|---|---|---|---|
| ESR 1st | 25.6 ± 19.31 | 81.73 ± 46.07 | 8.1 ± 2.64 | < 0.001 |
| ESR 2nd | 48.66 ± 31.84 | 111.6 ± 43.06 | 15.96 ± 4.78 | < 0.001 |
| CRP | 19.66 ± 20.85 | 18.86 ± 32.41 | 2.7 ± 1.8 | 0.006 |

JRA: juvenile rheumatoid arthritis; SLE: systemic lupus erythematosus; ESR: erythrocyte sedimentation rate; CRP: C- reactive protein; SD: standard deviation.

**Table-2**: Comparison between JIA, SLE and the controls as regards lipid profile.

| Lipid profile | Group I (JIA), n=15 | Group II (SLE), n=15 | Group III (Control), n=30 | P-value | | |
|---|---|---|---|---|---|---|
| TC: Mean ± SD | 171.8 ± 28.3 | 235.9 ± 90.4 | 141.6 ± 14.8 | < 0.001 | | |
| | | | | I vs. II | I vs. III | II vs. III |
| | | | | 0.002 | 0.124 | < 0.001 |
| TG: Mean ± SD | 95.4 ± 30.95 | 147.1 ± 42.1 | 87.7 ± 18.29 | < 0.001 | | |
| | | | | I vs. II | I vs. III | II vs. III |
| | | | | < 0.001 | 0.680 | < 0.001 |
| HDL: Mean ± SD | 53.4 ± 6.58 | 49.76 ± 7.06 | 55.03 ± 3.28 | 0.011 | | |
| | | | | I vs. II | I vs. III | II vs. III |
| | | | | 0.157 | 0.559 | 0.008 |
| LDL: Mean ± SD | 99.4 ± 25.25 | 154.9 ± 84.1 | 69.1 ± 15.37 | < 0.001 | | |
| | | | | I vs II | I vs III | II vs III |
| | | | | 0.004 | 0.092 | < 0.001 |

I vs. II: group I in comparison to group II, I vs. III: group I in comparison to group III, II vs. III: group II in comparison to group III; JRA: juvenile rheumatoid arthritis; SLE: systemic lupus erythematosus; ESR: erythrocyte sedimentation rate; CRP: C- reactive protein; SD: standard deviation.

**Table-3**: Correlation between DAI and lipid profile in JIA and SLE.

| Variables | JIA | | SLE | |
|---|---|---|---|---|
| | r | P- value | r | P- value |
| TC | 0.633 | 0.011 | 0.579 | 0.024 |
| TG | 0.523 | 0.046 | 0.559 | 0.030 |
| HDL | 0.133 | 0.636 | 0.020 | 0.943 |
| LDL | 0.548 | 0.034 | 0.533 | 0.041 |

r: correlation coefficient r>0.24 0r <-0.24 is significant; JRA: juvenile rheumatoid arthritis; SLE: systemic lupus erythematosus; DAI: Disease activity index; TC: total cholesterol; TG: triglycerides; HDL: high density lipoprotein; LDL: low density lipoprotein.

**Table-4**: Correlation between treatments of JIA and lipid profile.

| Group I (JIA) | TC | | TG | | HDL | | LDL | |
|---|---|---|---|---|---|---|---|---|
| | r | P-value | r | P-value | r | P- value | r | P-value |
| Steroid dose (n=6) | 0.915 | 0.010 | 0.122 | 0.818 | -0.234 | 0.655 | 0.911 | 0.012 |
| Steroid duration (n=6) | -0.194 | 0.713 | 0.789 | 0.062 | 0.338 | 0.512 | -0.355 | 0.489 |
| MTX duration (n=13) | 0.126 | 0.683 | 0.212 | 0.486 | 0.301 | 0.317 | 0.005 | 0.988 |
| Antimalarial dose (n=12) | 0.041 | 0.899 | 0.105 | 0.745 | 0.300 | 0.344 | -0.062 | 0.848 |
| Antimalarial duration (n=12) | 0.028 | 0.931 | 0.121 | 0.708 | 0.249 | 0.436 | -0.067 | 0.836 |
| Salazopyrin dose (n=3) | 0.711 | 0.497 | 0.749 | 0.461 | -0.500 | 0.667 | 0.327 | 0.788 |
| Salazopyrin duration (n=3) | 0.965 | 0.170 | -0.199 | 0.873 | -1 | <0.001 | 0.982 | 0.121 |

r: correlation coefficient r>0.24 0r <-0.24 is significant; JRA: juvenile rheumatoid arthritis; SD: standard deviation; TC: total cholesterol; TG: triglycerides; HDL: high density lipoprotein; LDL: low density lipoprotein; MTX: methotrexate.

**Table-5**: Correlation between treatment of SLE and lipid profile.

| Group II (SLE) | TC | | TG | | HDL | | LDL | |
|---|---|---|---|---|---|---|---|---|
| | r | P value | r | P value | r | P value | R | P value |
| Steroid dose (n=7) | -0.564 | 0.056 | 0.378 | 0.226 | -0.239 | 0.455 | -0.558 | 0.059 |
| Steroid duration (n=7) | 0.964 | <0.001 | -0.160 | 0.619 | 0.316 | 0.317 | 0.957 | <0.001 |
| Otherttt duration (n=7) | 0.688 | 0.007 | -0.238 | 0.413 | 0.242 | 0.405 | 0.682 | 0.007 |

r: correlation coefficient r>0.24 0r <-0.24 is significant; SD standard deviation; TC: total cholesterol; TG: triglycerides; HDL: high density lipoprotein; LDL: low density lipoprotein; TTT: treatment.

**Table-6**: Comparison of intima media thickness (IMT) between case and control groups.

| Parameters | Case group (n = 30) | Control group (n = 30) | P-value |
|---|---|---|---|
| Right IMT (mm) Range Mean ± SD | 0.35-0.56<br>0.42±0.03 | 0.30-0.40<br>0.31±0.02 | 0.0001 |
| Left IMT (mm) Range Mean ± SD | 0.36-0.49<br>0.42±0.02 | 0.31-0.41<br>0.32±0.02 | 0.0001 |
| Mean IMT (mm) Range Mean ± SD | 0.39-0.50<br>0.42±0.01 | 0.31-0.41<br>0.32±0.02 | 0.0001 |

SD: standard deviation.

## 4- DISCUSSION

JIA is the most common rheumatic disease in childhood and represents a major cause of functional disability in children (2). Chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematous had been proven to have a higher risk of premature coronary artery disease (CAD) (5). Abnormal lipoprotein levels play an important role in atherosclerotic processes that can be related to autoimmune disease. The risk to develop atherosclerosis increases progressively with increasing low-density lipoprotein cholesterol (LDL-C), and hypertriglyceridemia levels and declines with increased levels of high-density lipoprotein cholesterol (HDL-C) (11, 12). Premature myocardial infarction in patients with SLE, was observed, many studies have demonstrated a significantly increased morbidity and mortality from CVD in SLE. The incidence of CAD in SLE patients has been estimated to be 50-fold higher than in age and gender matched controls without SLE. In several studies, CVD was the leading cause of death in these patients. Scintigraphy studies, electron beam computerized tomography, and autopsy have shown a high prevalence of subclinical CAD. Myocardial infarction from CAD may occur in young patients with SLE (13). Our study aimed to clarify the cardiovascular risk in children with JRA and SLE, and its relation to lipid profile and disease activity index. In the present study as regards disease markers and disease activity, ESR (1st hour, 2nd hour) was higher in JIA and SLE patients in comparison to control group ($p<0.001$); also CRP levels were significantly higher in both patients groups compared to controls ($p=0.006$). These findings in JIA are in accordance with those of Wu et al. (14), and Ki et al. (15) who reported that the levels of ESR and CRP in active JIA are variable. The findings in SLE are in accordance with those of Habibi et al. (16) who reported that during acute exacerbations, the ESR may be elevated. CRP elevations are usually not seen inactive lupus, except in superimposed serositis, arthritis or infection.

In the present study, with regard to lipid profile comparison of TC, TG, LDL, and HDL in JIA group and control group revealed no significant difference. These findings are in accordance with Elizabeth et al. (17), and Thelma et al. (18), who failed to show any significant abnormalities of the lipid profile in individuals with JIA. In contrast, Gonçalves et al. (19), found reduced levels of HDL, and increased levels of triglycerides in 51 children with JIA compared with healthy controls. The reasons for the discrepant data between these studies are not clear, but it is possible that the observed variability in lipid

profiles relates to the variable disease subtypes and the levels of disease activity, which may impact on the composition of lipid fractions in the blood as in the study of Dursunoğlu et al. (20). In the present study, regarding lipid profile, there was high significant difference between SLE patients and controls in TC, TG, LDL ($p<0.001$), and in HDL ($p<0.008$). These findings are in accordance with the results of Sarkissian et al. (21), and Sarkissian et al. (22), who reported that the highest levels of TC, LDL, TG, and the lowest levels of HDL were found at diagnosis, prior to onset of therapy. On the contrary, Ardoin et al. (23) found that mean TG, LDL, and HDL levels were in the normal ranges. The most common lipid abnormality was also elevated TG levels, found in nearly 30% of subjects. The differences between the studies were probably the result of the disease activity and duration or type of immunosuppressive therapies of patients. Disease Activity Index (DAI) showed significant positive correlation between DAI in group 1 with TC ($r=0.633$, $p=0.011$), TG ($r=0.523$, $p=0.046$), and LDL ($r=0.548$, $p=0.034$), but no significant correlation with HDL ($r=0.133$, $p=0.636$).

These findings are in agreement with the studies of Thelma et al. (18) who observed increases in the TC and LDL-C levels as well as decreases in the HDL-C levels in the JIA group compared to the control group. Also, there was statistically significant positive correlation in group 1 between steroids doses with TC ($r=0.915$, $p=0.010$), LDL ($r=0.911$, $p=0.012$), and negative significant correlation between salazopyrin duration with HDL ($p<0.001$). These findings are in agreement with studies of Thelma et al. (18) who found that the levels of HDL were higher in the patients that were using corticosteroids; while, the direct effect of these agents on lipid metabolism suggests that glucocorticoids are pro-atherogenic. The anti-inflammatory action of the corticoids may counteract the lipid changes caused by the inflammation, thus resulting in a more benign lipid profile. On the contrary, these findings are in disagreement with studies of (Breda et al. (24), Vlahos et al. (25), who reported contradictory findings of active inflammatory lipid profile of high TGs and VLDL and lower levels of HDL, LDL and TC in JIA patients due to different disease subtypes, disease activity levels and corticosteroid doses. From previous works it seems difficult to determine the effect of disease and disease activity on the lipid profile in each distinct JIA subtype. Results of our study revealed that there was a statistically significant positive correlation between DAI in SLE patients with TC ($r=0.579$, $p=0.024$), TG ($r=0.559$, $p=0.030$), and LDL ($r=0.533$, $p=0.041$), but no significant correlation with HDL ($r=0.020$, $p=0.943$).

Also, significant positive correlation between steroids durations, and TC ($r=0.964$, $p<0.001$), LDL ($r=0.957$, $p<0.001$), and positive significant correlations between other treatments durations with TC ($r=0.688$, $p=0.007$), and LDL ($r=0.682$, $p=0.007$). Our results are in agreement with Sarkissian et al. (22), who found that reductions in the prednisone dose were generally associated with a decrease in cholesterol, LDL, triglycerides and an increase in HDL, which was consistent with the increased levels of triglycerides, LDL, and cholesterol; and corticosteroids can inhibit receptor uptake and the internalization and degradation of LDL particles (23). On the contrary, the cross-sectional APPLE trial of Ardoin et al. (23), who found mean TG, LDLC, and HDL-C levels that were in the normal ranges because of APPLE subjects had low SLE disease activity at baseline, which may have limited the ability to identify effects of active disease on lipid profiles. The most common lipid abnormality was also elevated TG levels, found in nearly

30% of subjects. Barsalouet al. (26) suggested that disease control is the most important factor to control dyslipidemia in SLE. RA itself was an independent risk factor for increased carotid IMT. Importantly, long-term combined treatment with MTX and chloroquine had favorable impact on IMT values. This observation may indicate that chronic inflammation, as a basic feature of RA, has an important role in accelerated atherosclerosis (27, 28).

## 5- CONCLUSION

In conclusion, children with rheumatologic diseases showed significant lipid profile changes with evidence of increment in intima media thickness in those patients. These findings carry high risk of accelerated arthrosclerosis and cardiovascular events, in rheumatologic children. So, continuous monitoring of lipid profile can decrease mortality and co-morbidity. Also, disease activity and corticosteroid use lead to alteration of lipid profile, indicating that optimal control of atherosclerotic changes can be achieved using minimal effective dose.

## 6- ABBREVIATIONS

**JIA**: Juvenile Idiopathic Arthritis,
**SLE**: Systemic Lupus Erythematosus,
**DAI**: Disease Activity Index,
**HDL**: High Density Lipoproteins,
**LDL**: Low Density Lipoproteins,
**ESR**: Erythrocyte Sedimentation Rate,
**CRP**: C - reactive protein,
**TC**: Total Cholesterol,
**TG**: Triglycerides,
**MTX**: Methotrexate,
**IMT**: Intima Media Thickness,
**LDL-C**: low-density lipoprotein cholesterol,
**LDL-H**: High-density lipoprotein cholesterol,
**VLDL-C**: Very Low-Density Lipoprotein Cholesterol,
**Apo A-1**: Apo lipoprotein,
**ILAR**: International League of Associations for Rheumatology,
**ACR**: American College of Rheumatology.

## 6- CONFLICT OF INTEREST: None.

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