

Serum Lipid Profiles in Pediatric Systemic Lupus Erythematosus Patients: A Study from Bangladesh

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Abstract: Aim: To assess the lipid profile in pediatric SLE (pSLE) patients in active disease state and compare it with inactive state. Methodology: It was an observational study carried out in the Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka-1000, Bangladesh from January 2013 to June 2014. A total 30 patients fulfilling the ACR 1997 criteria were enrolled in this study. Age and sex matched 15 controls were also included. Lipid profiles were measured at diagnosis, at 3 months follow up and at 9 months follow up. Results: At the time of diagnosis, pSLE patients' mean triglyceride level and HDL cholesterol levels were significantly abnormal. At 3 three months follow up, when disease activity was high and patients were on high dose steroid therapy, there was increased total, LDL and HDL cholesterol level. At 9 months follow up when most of the patients had inactive disease and were on low dose steroid, all the lipids were within normal range. Comparison of active disease group with inactive disease group at 9 months found significant improvement of total cholesterol, triglycerides and HDL cholesterol levels. Conclusion: Control of SLE seems to be the most important factor in normalizing the lipids.

Keywords: Lipid Profile, Systemic Lupus Erythematosus Disease Activity Index, Dose of Steroid

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens, leading to inflammatory damage of many target organs including the skin, joints, kidneys, blood cells, blood vessels and the central nervous system [1]. With increased survival of SLE patients, premature atherosclerosis is being recognized as a leading cause of mortality and morbidity [2]. The exact mechanism of this accelerated atherosclerosis remains unclear [3]. Atherosclerosis is a complex pathological process, with dyslipidaemia and inflammation fundamental to all stages of plaque evolution [4].

Lipid abnormalities in SLE patients may be due to disease process itself and also due to drug treatment like steroids [1].

Lipid profile may also be changed in different disease activity levels and in different prednisolone doses [5]. Levels of total cholesterol and LDL are mainly associated with the dose of prednisolone and high disease activity. Changes in HDL are usually associated with active SLE and a high dose of prednisolone [6]. It was found that changes in triglyceride levels were mainly associated with changes in disease activity. Low level of HDL cholesterol was associated with active SLE, whereas the dose of prednisolone was associated with increased levels of HDL cholesterol [5]. A recent study showed that lupus nephritis was more common in those patients with abnormal total cholesterol (TC) and TG levels at diagnosis [7]. No study so far has been done regarding lipid profiles in pediatric systemic lupus erythematosus (pSLE) patients in Bangladesh.

This study was carried out with the objectives of assessing the lipid profiles in pSLE patients during active and inactive

disease state in a tertiary care hospital in Bangladesh.

2. Methodology

It was an observational study carried out in the Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka. All the new patients fulfilling the ACR 1997 criteria of pSLE [2] attending the Department of pediatrics, BSMMU, during the period of January 2013 to June 2014 were purposively enrolled in the study. A total number of 30 patients were enrolled who subsequently completed at least 9 months of follow up. Age and sex matched 15 apparently healthy controls were taken for comparison of lipid profiles at a single time point at diagnosis. Pediatric SLE cases, previously treated with oral prednisolone and intravenous methylprednisolone within 1 month of lipid measurements were excluded from the study. Exclusion criteria also included pSLE patients previously treated with lipid lowering drugs, history of diabetes mellitus, thyroid disease and familial hyperlipidemia. After fulfilling the inclusion criteria, detailed history was taken and recorded in the questionnaire. Information included age, sex, weight, body mass index, duration of disease, family history of hyperlipidaemia, treatment with lipid lowering drugs and steroids. Physical examination findings, laboratory investigations, fasting serum lipid profiles and systemic lupus erythematosus disease activity index (SLEDAI) were also recorded in the questionnaire. The questionnaire was successfully pre-tested among 10 pediatric SLE patients before the study.

After enrollment of cases and controls, fasting lipid profiles were measured after overnight fasting and consumption of normal diet for previous 2 days (without fat restriction). Fasting lipid profiles included total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL). Lipid profiles for SLE cases were measured 3 times: at enrollment, at 3 months and finally at 9 months after diagnosis. Each time SLEDAI score was also assessed. At diagnosis all the SLE patients were given protocolized management of SLE which included general measures and drug treatment. Drug treatment included intra venous methyl prednisolone followed by oral prednisolone or only oral prednisolone, hydroxychloroquine, calcium, vitamin D, folic acid and intra venous cyclophosphamide when indicated. Patients were followed up initially monthly for 3 to 6 months and later on 2 to 3 monthly as required. Dose of prednisolone was reduced or adjusted by pediatric rheumatologists according to protocolized management.

For the analysis of lipid levels based on different disease states, operational definitions included 3 disease states according to SLEDAI scores and prednisolone dosage as follows [5]:

1. At diagnosis: Patients were not receiving any steroid medication but SLEDAI score was > 4 .

2. Active disease state: Patients had both SLEDAI score > 4 and their prednisolone dose was > 12.5 mg/day for a

period of 3 months or more prior to lipid measurement.

3. Inactive disease state: Patients had both a SLEDAI score ≤ 4 and their prednisolone dose was ≤ 12.5 mg/day for a period of 3 months or more prior to lipid measurement.

All the data were presented in tabulated form and were analyzed using computer based program Statistical Package for Social Science (SPSS) for Windows version 15. Data were expressed as mean (SD). Unpaired and paired t test were done to measure the level of significance (< 0.05).

3. Results

Average age of cases and controls were 11.55 years and 11.73 years respectively. In both the groups, female: male ratio was 14:1. Mean disease duration of cases was 5.4 months. Average BMI was 13.80 ± 2.3 kg/m² in cases and 16.20 ± 2.4 kg/m² in control group. Mean SLEDAI score was 17.5 ± 7.4 in cases at diagnosis (Table 1).

Table 1. Demographic Characteristics of Pediatric SLE Patients (n=30) and Controls (n=15).

| Characteristics | Cases (n=30) | Controls (n=15) |
|----------------------------------|------------------|------------------|
| Age (in years) | | |
| Range | 5 - 16 | 8 - 16 |
| Mean \pm SD | 11.55 ± 3.03 | 11.73 ± 2.05 |
| Sex | | |
| Female | 28 | 14 |
| Male | 2 | 1 |
| Female: Male | 14: 1 | 14: 1 |
| Disease duration (in months) | | |
| Range | 1.5-18 | |
| Mean \pm SD | 5.40 ± 4.17 | |
| Average BMI (kg/m ²) | 13.80 ± 2.3 | 16.20 ± 2.4 |
| Average SLEDAI score | 17.5 ± 7.4 | |

Table 2 shows that mean total cholesterol level, triglycerides level and LDL levels were higher among cases than control group. But, HDL cholesterol level was higher in control group. Difference of triglycerides and HDL cholesterol levels between the two groups were statistically significant ($P < 0.05$).

Table 2. Comparison of Lipid Profiles Between pSLE Cases and Controls at Diagnosis.

| Lipid | Diseases (n=30) | Control (n=15) | p value* |
|-------------------|---------------------|--------------------|----------|
| Total cholesterol | 177.90 ± 69.09 | 148.13 ± 21.31 | 0.112 |
| Triglycerides | 235.53 ± 143.17 | 87.87 ± 27.65 | 0.001 |
| LDL Cholesterol | 100.13 ± 51.58 | 84.33 ± 18.01 | 0.140 |
| HDL Cholesterol | 35.97 ± 21.23 | 51.80 ± 14.56 | 0.013 |

Data was express as Mean \pm SD.

Unpaired t test was done to measure the level of significant.

Comparison of changes in lipid profiles among the pSLE cases shows that mean triglyceride level was significantly reduced from diagnosis to 9 months follow up and from 3 months to 9 months follow up. Total cholesterol level was significantly decreased from 3 months to 9 months. LDL cholesterol level was also decreased significantly from 3

months to 9 months (Table 3).

Table 3. Comparison of Changes in Lipid Profiles at Diagnosis and during Follow up ($n=30$).

| Parameters | At diagnosis Mean \pm SD | At 3 months Mean \pm SD | P value | At 9 months Mean \pm SD | P value a. at 3month vs. 9month | P value b. at diagnosis vs. 9month |
|----------------------|-------------------------------|------------------------------|---------|------------------------------|------------------------------------|---------------------------------------|
| Change in TG levels | 235.5 \pm 143.1 | 184.0 \pm 73.9 | 0.08 | 123.2 \pm 60.2 | <0.01 | <0.01 |
| Change in TC levels | 177.9 \pm 69.0 | 193.2 \pm 57.5 | 0.28 | 155.9 \pm 33.5 | <0.01 | 0.09 |
| Change in LDL levels | 100.1 \pm 51.5 | 108.1 \pm 41.9 | 0.41 | 85.7 \pm 27.2 | 0.006 | 0.15 |
| Change in HDL levels | 35.9 \pm 21.2 | 51.2 \pm 21.7 | 0.01 | 45.7 \pm 13.6 | 0.16 | 0.03 |

Data was express as Mean \pm SD.

Paired t test was done to measure the level of significant.

An improving trend of lipid profiles from baseline to 9 months follow up is shown in figure 1. At diagnosis 63.3%, 70%, 26.7% and 73.3% patients had abnormalities in total cholesterol, triglyceride, LDL cholesterol and HDL levels respectively. At 9 months follow up 20%, 16.7%, 6.7% and 33.3% of patients had abnormalities in total cholesterol, triglyceride, LDL cholesterol and HDL cholesterol respectively.

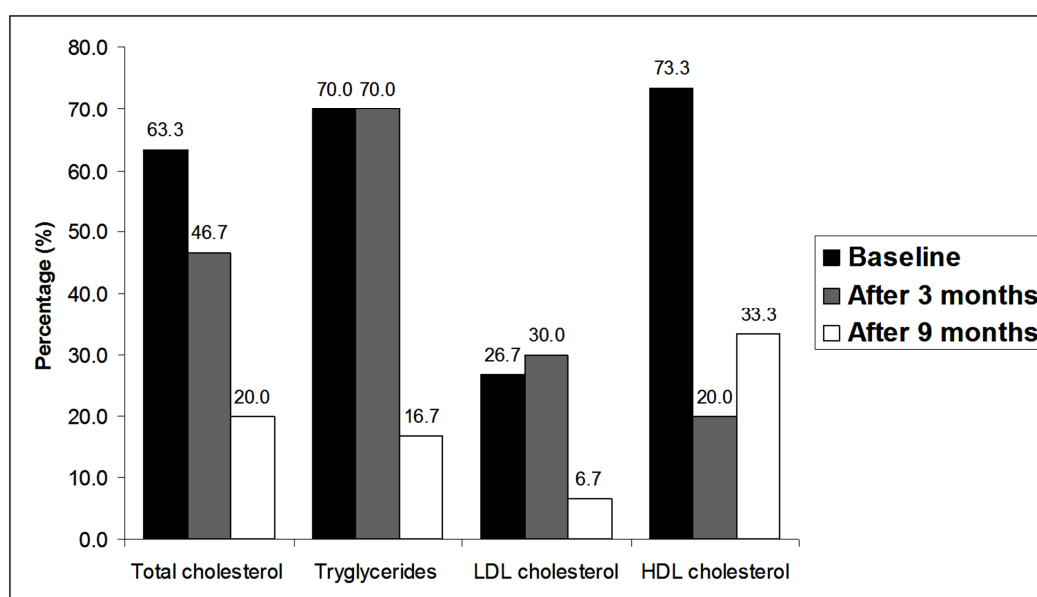


Figure 1. Abnormalities of Lipid Profile at Diagnosis and at Different follow up.

4. Discussion

Premature atherosclerosis has become a leading cause of death in SLE patients in later life after many years of active disease. Abnormal lipid profile might play an important role in this regard [8, 9]. American Academy of Pediatrics assumes that pediatric SLE patients may be at an even greater risk for coronary artery disease because of their earlier disease onset and more severe course [10]. Therefore, early diagnosis, treatment and prevention of dyslipidemia are very important aspects of treatment in patients with SLE.

Previous studies done among SLE patients reported that both the disease activity and steroid therapy may alter lipid profile in SLE cases [5, 6, 11]. However effect of each variables e.g. disease activity and steroid therapy is difficult to identify as because during high disease activity, high dose of steroid is also frequently administered. In this study average age of cases and controls were 11.55 years and 11.73 years respectively. In both the groups female: male ratio was

14:1. Mean disease duration was 5.4 months. Brunner *et al.* in their study [12] found that pediatric SLE cases were commonly diagnosed between the ages of 12 and 14 years and rarely before the age of 5 years. Our findings were also similar.

SLE cases at diagnosis (active by SLEDAI score without steroid therapy) had higher levels of total cholesterol, triglycerides and LDL cholesterol. HDL cholesterol was lower among the cases. None of the control group had any lipid abnormalities. Difference of triglycerides level and HDL cholesterol level was significant among cases and controls. Ettinger *et al.* in their study found similar results, where patients with SLE had higher levels of plasma triglyceride, total cholesterol and low-density lipoprotein cholesterol than control subjects but lower HDL cholesterol levels [13]. Siripaitoon *et al.* in their study also found similar results showing a significant elevation of TG levels and significantly lower HDL cholesterol level in SLE patients than control [14]. Lipid abnormalities had been reported to occur in other studies as well [5, 13].

Following the initiation of steroid therapy at high dose (at 3 months follow up), mean total cholesterol level and mean LDL cholesterol level was increased in the present study, though the differences were not significant. Triglyceride level was decreased (not significant). Only HDL level became significantly higher. Ettinger Jr. and Hazzard [15] in their study among healthy men found that prednisolone therapy significantly increased the levels of LDL cholesterol and HDL cholesterol. Sarkissian et al [5] in their study on pediatric SLE patients found that changes in triglycerides levels were mainly associated with disease activity but changes in total cholesterol and LDL cholesterol levels were mainly associated with prednisolone dosage and not disease activity. They also found that low levels of HDL cholesterol were associated with active SLE, whereas prednisolone dosage was associated with increased levels of HDL cholesterol. Our results were similar with Sarkissian et al study [5]. Sarkissian et al in a different study [6] also found a positive association of triglyceride level with proteinuria. The present study did not look into the relationship of triglycerides with proteinuria.

Comparison of individual lipids (triglycerides, total cholesterol, LDL cholesterol and HDL cholesterol levels), at different time intervals (at diagnosis, at 3 months and at 9 months) show a significant decrease of triglyceride levels from 3 months to 9 months and also from diagnosis to 9 months. Significant improvement of total cholesterol level was found only from 3 months to 9 months. Similarly significant improvement of LDL cholesterol level was found from 3 months to 9 months. Significant improvement of HDL cholesterol level was found from diagnosis to 3 months and from diagnosis to 9 months follow up (Table 3).

Analysis of abnormalities in lipid profile at diagnosis and at different follow up shows a gradual improving trend of total cholesterol and triglycerides levels among SLE patients. LDL cholesterol abnormality was slightly higher at 3 months but HDL cholesterol abnormality was higher at diagnosis than 3 months. It is well established that steroid increases LDL and HDL cholesterol levels [15].

Previous studies demonstrated that active systemic inflammation was associated with low HDL levels. However, high dose prednisolone therapy was associated with increases in HDL levels, which could be attributed to the increase in lipoprotein lipase and lecithin-cholesterol acyltransferase activities [16,17]. Thus, at 3 months follow up, higher levels of HDL cholesterol found in this study may be the result of a balance between the opposing effects of active disease and corticosteroids level.

Almost similar findings were found at 9 months follow up, where significant changes leading to improvement of mean total cholesterol and mean triglyceride levels and LDL cholesterol levels were found. It is already known that prednisolone therapy increases HDL cholesterol level [6] and disease activity of SLE itself has a relationship with HDL levels [11]. It is to be mentioned here that at 9 months follow up, 90% patients were in inactive disease state and were on low dose steroid therapy. So, it might happen that during

inactive disease state due to lower dose of prednisolone, HDL cholesterol level was lower. If only disease activity is considered, this study found that mean total cholesterol level, TG level and HDL cholesterol level was significantly higher among active group than inactive disease state group at 9 months.

Lipid profile abnormalities at diagnosis were present in more than 73% pediatric SLE patients in our series. Majority had lower HDL levels (73.3%) followed by higher triglycerides level (70%). High total cholesterol level was found in 63.3% cases and LDL in 26.7% cases (Fig 1). In this study, we also found that the interaction of disease activity and steroid therapy dose was quite complex and effect on each lipid may be important.

Sarkissian et al. assessed the long term effect of inactive disease and stable dose of steroids on lipid profiles [6]. In their study after 2 years of longitudinal follow up, pediatric lupus patients had normal and relatively constant levels of mean LDL and total cholesterol. Our study had a shorter duration and so, long term effects could not be assessed. Nevertheless this study found that inactive disease had most important role in normalizing lipid levels. This finding was consistent with previous studies showing that control of SLE appeared to improve the important lipid abnormalities [5, 6, 18].

The findings of the present study are important for determining the prognosis of pediatric SLE patients indicating the need of attention towards measurement of lipid profiles during management and follow up period. Serial measurements of serum lipids at different doses of steroid therapy are essential to dissect the complex nature of role of active disease and steroid therapy on lipid profiles.

5. Conclusion

Disease activity of SLE itself is associated with abnormal lipid profiles, more so in triglycerides and HDL cholesterol levels. Steroid therapy increases total cholesterol, LDL cholesterol and HDL cholesterol level. Steroid also decreases triglyceride level. Inactive disease and lower dose of steroid therapy normalizes all the lipid levels. Control of disease activity in SLE seems to be the most important factor in normalizing the lipid profile.

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