**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. SLE in children and adolescents (pSLE) may have a great variability in disease presentation and course. pSLE tend to have more severe and more aggressive disease course than adult SLE patients, and often presents with major organ system involvement, including renal, neuropsychiatric (NP) and haematological involvement. Among the general clinical characteristics, constitutional symptoms such as unexplained fever, malaise and weight loss are present in 40-90% of cases and are the most common manifestations in pSLE. These manifestations may be seen throughout the course of the disease or intermittently. In Bangladesh one study found that common clinical presentations of pSLE included general weakness/fatigue (91%), fever (83%), arthralgia/arthritis (74%), oral ulcer (73%), and skin rash (71%).

Lipid abnormalities in patients with SLE are common. It may occur due to disease process itself and also due to drug treatment like steroids. In SLE patients there is accelerated atherosclerosis. The exact mechanism of this accelerated atherosclerosis remains unclear. However, disease activity with its immunologic events, the presence of anticardiolipin antibodies and hyperlipidaemia contribute to development of atherosclerosis. The aim of this review is to discuss the lipid abnormalities in pSLE patients and its relationship with different disease activity states. This review also intends to discuss the role of steriod and hydroxycholoroquine on lipid metabolism in these patients during treatment.

**Mechanisms of Lipid abnormalities in SLE**

Lipid abnormalities in patients with SLE are very common and likely to be one of the causes of premature atherosclerosis in these patients. In SLE patients especially with renal involvement, serum lipid levels are elevated for two reasons. Hypoalbuminemia stimulates generalized hepatic protein synthesis, including synthesis of lipoproteins. In SLE patients also have disturbances in lipid metabolism that are characterized by decreased lipolysis and also decreased removal of chylomicron remnant from the plasma. High levels of systemic inflammation found in conjunction with SLE result in an increased burden of oxidative stress. Increased oxidative stress can trigger a broad range of pro-atherogenic lipid modifications, including the formation of oxidised LDL (oxLDL), conversion of anti-inflammatory high density lipoprotein (HDL) into pro-inflammatory HDL and alteration of the function of key enzymes involved in lipid metabolism and function. The oxidation of LDL is particularly interesting in SLE, as oxidation affects not only the lipid component of the lipoprotein but also components such as cardiolipin. Antibodies directed against oxidized cardiolipin (anti-phospholipidantibodies) are increased in a number of SLE patients, predominately those exhibiting features of co-existent anti-phospholipid syndrome (APS). SLE patients have high levels of antibodies against oxLDL, which may accelerate the uptake of LDL into the endothelial wall. In addition, there is expanding evidence that antibodies against oxLDL may cross-react with IgM and IgG anticardiolipin antibodies, thus further escalating cerebrovascular disease risk. oxLDL forms complexes with â2-glycoprotein I, which have been shown to amplify arterial thrombosis in patients with APS and this, may also be a pro-atherogenic mechanism in SLE patients who are positive for APS antibodies.

**Premature Atherosclerosis and Lipid Abnormalities in SLE patients:** Cardiovascular disease with premature atherosclerosis is common in patients with SLE. Enhanced lipid peroxidation may
play an important role in SLE, especially with respect to the premature atherosclerotic process. A number of traditional and nontraditional atherosclerotic risk factors, including lipid abnormalities, altered endothelial function, nephritis, and proteinuria have been implicated in the development of premature atherosclerosis in patients with pSLE. Reports of myocardial perfusion deficits, altered vascular reactivity, and carotid intima-media thickness in SLE patients suggest that even during adolescence pediatric patients are at risk for premature atherosclerosis, myocardial infarction, and cerebral vascular events. It is likely that the major risk factor for premature atherosclerosis is the chronic inflammatory process of pSLE itself. The risk is likely to increase with the use of corticosteroids as the mainline of pSLE treatment. Atherosclerotic vascular disease (ASVD), including both coronary artery disease (CAD) and cerebro-vascular disease, represents a major cause of disability and death in SLE cases.

Disease activity of SLE and lipid profile
Dyslipoproteinemia of active disease consists of depressed HDL cholesterol with elevated very low density lipoprotein (VLDL) cholesterol and triglyceride (TG) levels.

Sarkissian T. et al. study found that, active SLE patients had proatherogenic lipid profile and also found that, at the time of diagnosis, the mean levels of total cholesterol, LDL cholesterol, and triglycerides were highest, whereas mean levels of HDL cholesterol were lowest. The percentage of patients with abnormal triglyceride value was highest at diagnosis, decreased at year one, and then remained relatively constant thereafter. The mean total cholesterol and LDL cholesterol levels decreased at year one as compared with the time of diagnosis and then remained relatively constant. The lowest mean HDL cholesterol levels were found at the time of diagnosis, and these values increased with time.

Kakati et al. in their study measured fasting lipid profiles in 30 SLE patients. Among them 19 patients (63.3%) had dyslipidaemia. Another study showed that at least one lipid abnormality was present in the majority of patients (63%), an elevated triglyceride level being the most common (62%) lipid abnormality. Olusi et al. study found that patients with SLE had significant dyslipidemia, characterized by elevated plasma triglycerides, LDL cholesterol, Apoprotein B, triglyceride: high-density (HDL) lipoprotein cholesterol ratio, and decreased plasma concentrations of HDL cholesterol. Siripaitoon B et al. study found a significant elevation of TG levels and significantly lower of HDL cholesterol level in SLE patients than control. A recent study done in our country found that SLE cases at diagnosis (active by SLEDAI score without steroid therapy) had higher levels of total cholesterol, triglycerides and LDL cholesterol than control. HDL cholesterol was also lower among these cases than controls. But at nine months of follow up, when most of the cases had inactive disease and were on low dose steroid therapy, all the mean values of lipids (total cholesterol, triglycerides, LDL and HDL cholesterol) were within normal range.

Role of steroid on lipid profile in pSLE
SLE patients, particularly children, had a higher fat mass and lower lean mass than healthy controls and corticosteroid use was an independent predictor of increased fat mass. Ettinger Jr. and Hazzard in their study among healthy men found that prednisolone therapy significantly increased the levels of LDL cholesterol and HDL cholesterol. Ettinger et al. study found that SLE patients treated with prednisolone had higher triglyceride, total cholesterol and LDL cholesterol than other SLE patient not receiving prednisolone. The study done in our country found that at three months follow up period, when SLE children were on high dose steroid therapy, there were increase of mean total cholesterol, LDL cholesterol and HDL cholesterol. Triglyceride level was decreased at that time.

Examining the relationship between glucocorticoid (GC) use and dyslipidaemia at times found conflicting results. While clinical trials involving patients with SLE had shown prednisone doses >10 mg/day to be associated with hyper-lipidaemia, trial conducted in patients with rheumatoid arthritis found no adverse effect of prednisone (20 mg/day tapered to 5 mg/day over 3 months) on serum lipids after adjustment for other risk factors. In fact, findings from a study examining data from 15,004 participants in the Third National Health and Nutrition Examination Survey suggest that glucocorticoids use may have a beneficial effect on lipids in adult’s 60 years of age. Despite the conflicting evidence, regular monitoring of lipids as well as other traditional risk factors for CVD is recommended in patients using glucocorticoids at high doses or for prolonged periods.
In another study, comparison of lipids at different prednisolone dosages and disease activity levels revealed that changes in triglyceride levels were mainly associated with changes in disease activity, whereas changes in both total cholesterol and LDL cholesterol levels were associated with changes in prednisolone dosages and not disease activity. Low levels of HDL cholesterol were associated with active SLE, whereas the prednisolone dosage was associated with increased levels of HDL cholesterol. The study done in our country found that control of disease activity in SLE was the most important factor in normalising the lipid profile.

In conclusion disease activity of SLE is the most important predictor of low levels of HDL cholesterol and high levels of total cholesterol, LDL and tryglyceride levels. On the other hand, steroid increases HDL, total cholesterol and LDL levels. Increases in the levels of HDL were mainly associated with the control of disease activity. However, control of disease activity is the single most important factor for normalization of lipid levels in SLE patients both in adults and children.

Role of hydroxychloroquine on lipid profile in pSLE
Hydroxychloroquine (HCQ) is a very important drug in the management of SLE (adult and childhood) having multiple properties including: immunosuppressive, anti-inflammatory and sunblocking effects. It is also reported to have anti-platelet activity and lipid lowering effects. Short-term use of hydroxychloroquine has a beneficial effect on lipids, particularly in the reduction of total cholesterol and LDL cholesterol levels, and might also help to reduce the cardiovascular risk in SLE. The Canadian Hydroxychloroquine group evaluated the ability of long term hydroxychloroquine to prevent major flares in quiescent SLE, and found that it had a long term effect against major flares, reducing the risk by 57%. There is also high level of evidence that antimalarials (HCQ) increase long term survival of lupus patients, moderate evidence of protection against irreversible organ damage, bone mass loss and thrombosis.

Management of lipid abnormalities in SLE
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. So early management of dyslipidaemia is important to prevent the risk of premature atherosclerosis in SLE patients.

Management should include:

a) Dietary management
b) Drug therapy

a) Dietary Management:
- Increase dietary fiber intake.
- Reduce saturated fat intake to provide at least 30% of total fat intake.
- Reduce total fat intake to provide not more than 30% of total energy intake.
- Increase consumption of oily fish.
- Eat at least five portions of fresh fruit or vegetables/day.

b) Drug therapy:
Drugs to lower blood lipid levels should be considered for all patients who have hyperlipidaemia inspite of the above dietary measures and treatment of secondary causes of dyslipidaemia. There are several groups of lipid-lowering drugs with different actions. Generally the first line of treatment is statin if the LDL cholesterol is elevated, and a fibrate if hypertriglyceridermia or if the HDL cholesterol is low.

Monitoring of lipid profiles every six months in SLE patients is strongly recommended.

Conclusion
Active disease state in SLE patients may cause altered lipid levels, especially triglycerides and HDL cholesterol. Besides, high dose of steroid therapy in these patients increases total cholesterol, LDL cholesterol and HDL cholesterol levels. Controlling the disease activity, maintenance of remission in SLE patients as well as administration of lipid-lowering agents based on the lipid abnormalities may lower the risk of premature atherosclerosis in these patients. Hydroxychloroquine also has important beneficial effects on lipid abnormalities in SLE patients. So physicians should be careful regarding the use and monitoring of steroid, hydroxychloroquine and lipid lowering agents for better prognosis in these patients.

References


16. Islam MM. Lipid profile in paediatric SLE patients in active and inactive state of disease. MD thesis 2015; Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh.


22. Cairoli E, Rebella M, Danese N, Garra V, Borba EF. Hydroxychloroquine reduces low-density lipoprotein cholesterol levels in systemic

