Over the past few decades survival in patients with SLE has gradually improved in the Western world. Under optimal conditions of diagnosis and supervised treatment, with good social support, life-expectancy can be as high as 90% at 10 years. Although there have been a dramatic improvement in the short term prognosis with proper immunosuppression and care of infection, the mortality rates in patients surviving for more than 5 years and specially for more than 10 years have not shown such gratifying improvement particularly in the developing countries. In the late 70’s the bimodal mortality in lupus erythematosus has been attributed to active disease or infections in first 5 years of onset and second peak of mortality due to consequences of therapy or atherosclerotic vascular disease. In 1985 this was further strengthened; patients of SLE in their late years die of causes other than the disease itself. The long-term consequences of drug treatment of SLE contribute to its late morbidity and mortality to a great way. Most of the long-term complications are the effects of aging, disease related life-style changes, atherosclerotic end-organ damage and quite often include drug-related complications and consequences of associated immune disorders. Early recognition and intervention may be needed to prevent such complications. The late complications of SLE are enumerated in Table 1.4

The acute events will not be discussed here. Common late complications which are drawing the attention of the clinicians recently are addressed below.

1. **Retinal toxicity:** The retinal toxicity usually develops following prolonged chloroquine therapy (10 years) in about 10 percent patients.5,6 The drug may be deposited in the cornea causing blurring of vision, photophobia and visual halos. These are reversible on withdrawal of the drug. Early retinal changes include macular oedema, increased pigmentation and loss of foveal reflex. Advanced macular depigmentation surrounded by concentric pigmentation represents bull’s eye lesion and these changes are often irreversible. Ischaemic optic atrophy and peripheral retinal depigmentation are late changes. Retinal toxicity is more common with chloroquine than hydroxychloroquin.7,8 Visual acuity, slit lamp examination and automated perimetry every 6 months helps in early detection of above changes and prevention of visual impairment. The prevalence of retinal toxicity is low in India.

2. **End-stage renal disease:** This may be due to progressive glomerulosclerosis with fibrocrescents, interstitial fibrosis, tubular atrophy (WHO class VI). The end-stage renal failure tends to occur in 5-10% patients of lupus nephritis.5,8 The therapeutic efficacy of potent immunosuppressive agents at this stage is less evident. Management is as per guidelines for patients with chronic renal failure. Tight blood pressure control, optimal use of ACE-inhibitors with monitoring of serum creatinine and serum potassium and protein-restricted diet (0.4-0.6 gm/kg/day) are recommended.9 Essentially these patients need renal support system with dialysis and renal transplantation soon. The major causes of death in patients with end-stage renal disease are coronary artery disease and opportunistic infections.

In a recent study,10 recurrence of nephritis in post-transplant recipient was studied. Ninety seven consecutive SLE patients receiving 10 renal transplants between 1984 to 1996 were evaluated. All the patients had received cyclosporine and these included 81 females and 16 males with mean age of 35 years. The average duration of pre-transplant dialysis was 34 months and the patients were on 63 months follow up. Pathological evidence of recurrence was observed in 9 patients with an average time of recurrence of around 3 years of which four had graft rejection needing re-transplantation.12

3. **Neuropsychiatric and neurocognitive dysfunction:** The clinical syndromes of neuropsychiatric SLE are extremely diverse and range from overt manifestations such as psychosis, seizure and stroke to subtle abnormalities of cognitive functions. The occlusive vasculopathies due to atherosclerosis and antiphospholipid antibody syndrome are major contributory factors. Neuropsychiatric dysfunction is frequent in late stage of SLE (as per ACR 1999 criteria) with variable prevalence rate of 12 to 87%13,14 These patients usually present with failing memory, increased speech disability and affective disorder. Follow-up is carried out by 11 items of Miniminal Scale Examination (MMSE) periodically. Also, ACR 1999 recommends a simple 1 hour neuropsychological test for assessment of cognitive dysfunction.14 The anatomical correlates of these are not often found though 95% of SLE patients have ‘subcortical’ deficits15 simulating more of Huntington’s disease than Alzheimer’s disease. Alternate

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**Table 1: Late complications of SLE**

<table>
<thead>
<tr>
<th>Acute event</th>
<th>Chronic morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>End-stage renal disease, dialysis, transplantation</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Atherothrombosis, venous syndromes, pulmonary emboli</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Osteonecrosis, osteoporosis</td>
</tr>
<tr>
<td>Cerebritis</td>
<td>Neuropsychiatric dysfunction</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Shrinking lung syndrome</td>
</tr>
</tbody>
</table>

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Ex-Prof. & Head, Medical College, Kolkata; Consultant Physician, Calcutta Medical Research Institute, Kothari Medical Centre, Kolkata.
explanations to the pathoimmunologic processes are depression, medications and poor sleep which affects patient’s ability to attend to task fully. The disruption of normal thought processes reduces short-term memory and capability as well as problem-solving ability.18 The affective disorder like depression is often co-existent with dementia. The atherosclerotic cerebrovascular disease may also enhance neurocognitive dysfunction. The antiphospholipid antibodies are also important risk factors for neurocognitive dysfunction. The steroid-psychosis is not an uncommon co-existent phenomenon. At times it is difficult to distinguish this from disease-related psychosis; however the therapeutic response to short course (48-96 hours) of escalated dose of steroid may resolve the issue. MRI is superior for localizing cerebral infarcts and haemorrhages. The microemboli detected by MRI and autopsy are strongly associated with CNS problems.17 CT scan reveals cortical atrophy which may be related either to CNS complications of SLE itself or to the use of corticosteroids for a long time. The SPECT (single photon emission computerized tomography) and MRS (magnetic resonance spectroscopy) have high sensitivity but lack specificity. There is hardly any specific role of immunosuppressive agents in the treatment of cognitive dysfunction.

4. **Shrinking lung syndrome:** These patients present with progressive dyspnoea in the background of normal chest examination and their prognosis is rather poor.15,19 Chest X-ray may reveal elevated diaphragm with normal lung fields.19 The possible underlying mechanisms include impaired function of respiratory muscles and skeletal system involved in respiration.20 Pulmonary function testing reveals restrictive defect. Some of the studies have demonstrated specific intercostal or diaphragmatic weakness and postmortem studies have shown that diaphragm is usually thinned out and fibrosed. The appearance of this condition in the natural history of SLE implies grave prognosis.

5. **Gonadal dysfunction:** Long term cytotoxic therapy in SLE patients who are mainly in the reproductive age group poses a high risk of gonadal dysfunction. In an interesting study21 70 premenopausal women suffering from SLE (excluding those patients who had renal failure or were receiving any hormone therapy) were included in the study. It was noted that the incidence of ovarian failure increased with the age of the patients (particularly beyond 30 years) and depended on the cumulative dose of cyclophosphamide. This complication may be prevented by short courses of therapy with lower doses of cyclophosphamide. The risk of sustained amenorrhea had been reported in 11-59 percent in this study. Overall incidence of ovarian failure was 26%. The mean cumulative cyclophosphamide dose was 28gm in the group with ovarian failure while it was 15gm in the group without ovarian failure. The incidence of ovarian failure according to age and cumulative dose of cyclophosphamide is shown in Table 2.21

The recovery of ovarian function is unpredictable. In very young patients consideration should be given for pretherapy ovum or sperm storage for future fertility. Conventionally azathioprine is recommended as cyclophosphamide-sparing agent for long-term therapy in order to preserve ovarian function.

### 6. Glucocorticoid-induced side effects:

These chiefly include hypertension,22 dyslipidemia,23 premature atherosclerotic vasculopathy,24 cataract,25 osteoporosis26 and neurocognitive dysfunction27 in SLE patients on long-term follow-up. Longer duration and daily dose of prednisolone in excess of 10mg are the key factors for adverse effects. Regular monitoring of body weight, BP, eyes, blood sugar, plasma lipids and annual DEXA scan of spine and femoral neck are mandatory.

### 7. Osteonecrosis: A definite association between osteonecrosis (ON) and SLE was first documented in 1960 and is now well-recognised.28 It is an important cause of acute pain in single joint in 10% of late stage SLE. In patients of SLE the disease is magnified in that, it not only involves the hips but often other joints like knee, shoulder and ankle. Osteonecrosis initiates in the epiphyseal bone and causes pain before any joint cartilage destruction is observed. The clinician should be aware of the risk factors29 and clinical findings in patients with SLE that allow early diagnosis of ON. Osteonecrosis of femoral head in patients with SLE ranges from 2-8% to 40% in large series. Bilateral hip involvement occurs in upto 90% of SLE patients with ON. Approximately 20% of these patients develop ON in other joints making the effects of this disease even more devastating.28 ON shows preponderance in male SLE patients. In an Indian study on avascular necrosis in 1999, 13 out of 502 SLE patients had avascular necrosis and hip was most commonly involved.31 Mechanisms that have been postulated for non-traumatic ON include arterial emboli or thrombosis, venous occlusion, vessel wall injury, increased intraosseous pressure and coagulation disorders.32 The major risk factors for ON in patients with SLE are: prednisolone therapy with doses greater than 20mg each day for a long time, evidence of end-organ effect of corticosteroid use and certain pathophysioligic variables such as vasculitis, Raynaud’s phenomenon and APLA syndrome.33-35 Exposure to corticosteroids, alcohol

### Table 2: Incidence of ovarian failure in systemic lupus erythematosus patients treated with cyclophosphamide according to age and cumulative cyclophosphamide dose

<table>
<thead>
<tr>
<th>Age at start of cyclophosphamide</th>
<th>Cumulative cyclophosphamide dose gms/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment years</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>0/15 (0)</td>
</tr>
<tr>
<td>30-39</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1/4 (25)</td>
</tr>
<tr>
<td>All</td>
<td>1/25 (4)</td>
</tr>
</tbody>
</table>
and tobacco abuse, disease duration above 4 years and presence of renal disease account for more than 90% of all known associated factors. However, only approximately 10 to 20% of patients with SLE having these risk factors develop the disease. Conventional x-ray of hips may miss early diagnosis when MRI will reveal osteonecrosis easily. Radionuclide bone scan also tends to make an early diagnosis. Decreased weight bearing with the use of stick, weight reduction and alendronate 10mg/day are recommended in early cases. More so, joint preserving procedures such as core decompression, bone grafting and osteotomies can be attempted with some success. Late diagnosis almost always necessitates total joint replacement, which should be avoided if possible in this young patient population and whose success rate in SLE is rather poor.

8. Osteoporosis: This is a common complication in patients receiving long-term glucocorticoid therapy. Glucocorticoids inhibits osteoblastic activity, stimulate osteoclastic activity, decreases calcium absorption thereby inducing secondary hyperparathyroidism. The muscle wasting caused by glucocorticoids contributes indirectly towards osteoporosis. Patients of SLE are at increased risk of osteoporosis due to avoidance of sunlight in order to prevent photosensitivity. Estrogen lack may be implicated in the bone loss that occurs in SLE. In addition, some patients of SLE have hyperprolactinemia which may further decrease circulating levels of estradiol or testosterone. Further, SLE frequently presents in young people before achieving of peak bone mass, thus reducing their chance of having normal bone mineral density. Pro-inflammatory mediators like IL-1, IL-6 and tumour necrosis factor may alter bone metabolism and influence the development of osteoporosis. Renal damage in SLE may result in an impaired ability to manufacture calcitriol leading to secondary hyperparathyroidism and increased osteoclastic bone resorption. Besides glucocorticoids, cyclophosphamide and azathioprine may be indirectly associated with osteoporosis due to gonadal failure. Annual DEXA scan of spine and femoral neck will help in early detection of loss of bone and diminished bone mineral density due to steroid-induced osteoporosis.

Osteoporosis can be prevented by advocating balanced nutritious diet with calcium and activated vitamin D supplementation, oestrogen replacement therapy (0.625 mg/d), weight bearing exercise and stoppage of smoking in all patients receiving long-term steroid therapy (osteoporosis prophylaxis). In SLE patients suffering from osteoporosis treatment with calcium 1000-1500 mg/day, vitamin D 0.50 to 1.0 µg/m d are advocated in specific subsets, where oestrogen replacement is not acceptable. Dehydroepiandrosterone (DHEA) 50-200 mg/day is also advocated as androgen replacement therapy for preventing steroid-induced osteoporosis.

9. Coronary Artery Disease: Over the years the mortality of SLE patients has decreased with the advent of corticosteroid therapy. However, with increased survival the incidence of ischaemic heart disease in lupus patients has been increasingly reported. In the John Hopkins cohort, 30% of lupus mortality was attributed to coronary artery disease with the average age of these patients who had one or more risk factors for CAD being 38.3 years. It has been increasingly observed that this accelerated atherosclerosis may not only be due to corticosteroids but may be directly contributed by lupus itself. The recent concept in the aetiopathogenesis of atherosclerosis in SLE patients involves three basic contributory mechanisms namely, immune-complex vasculitis, proatherogenic and procoagulative factors with accelerated atherothrombotic events.

1. The proatherogenic factors contributory to atherogenesis are:
   a. The common co-existing problem is hypertension and its mean prevalence has been reported in 28.8% of lupus patients.
   b. Lipid profile - In a study of 46 SLE patients elevated plasma triglycerides, LDL and total cholesterol are found. In another study it has been observed that a subgroup of SLE patients with persistently elevated total cholesterol in excess of 5.2 mmol/L are more likely to have higher disease activity. Moreover, decreased lipoprotein lipase in untreated SLE patients may explain elevated VLDL cholesterol. High lipoprotein(a) is also observed in SLE patients. Following prolonged corticosteroid use in SLE patients elevated total cholesterol, VLDL cholesterol and triglyceride levels are characteristic.
   c. Corticosteroid therapy is a well known risk factor for coronary artery disease due to significant changes in lipid profile, blood pressure and body weight. The therapy with prednisolone was shown to be significantly associated with coronary artery disease in SLE.

2. The procoagulant risk factors precipitating thrombus formation are:
   a. Antiphospholipid antibodies and anti-cardiolipin antibodies are promoters of thrombus formation complicating atheromatous plaque. These procoagulant factors in SLE decreases prostaglandin synthesis, increases thromboxane A2 secretion and directly damage endothelial cells. Hence thrombogenesis is enhanced.
   b. Anti-oxidised-LDL antibodies have been reportedly increased in 80% patients with SLE to promote plaque formation. There may be crossreaction between oxidized LDL antibodies and cardiolipin for plaque enhancement.
   c. Lipoprotein(a) is found to be present in 37% lupus patients which contributes to atherogenesis.
   d. In 15% of SLE patients, raised homocysteine concentration may be found and it has been recognised to be a risk factor for stroke and arterial thrombosis but no association has been found with venous thrombosis. It is found to be associated with low vitamin B12 and folic acid levels in these patients and some authors recommend its replacement in SLE patients. It is observed that prednisone therapy may raise homocysteine levels directly through its hormonal effects.

Interestingly, in the John Hopkins Lupus Cohort Study of 229 SLE patients, coronary artery disease (CAD) mainly caused by atherosclerosis occurred in 8.3% and...
The important risk factors for atherothrombotic vascular disorders in the above study include age beyond 45 years, hypertension, hyperlipidaemia, obesity, steroid overuse and antiphospholipid syndrome. Associated hypothyroidism indirectly contributed in these vascular diseases.

The late mortality beyond 10 years was in nine out of 142 patients followed in this series. The different causes as observed are shown in Table 4. In a study from North India the causes of death in SLE were observed as SLE-related 42%, infections 29%, vascular disease 6.5% and unknown 23%.51

Delaying or preventing late complications of SLE is achieved with the following steps in the long-term holistic care of the patients.52

a. Early screening of organs at risk and their assessment.

b. Life-style modification about diet, body-mass index and smoking.

c. Control of hypertension with ACE inhibitors or calcium antagonists.

d. Metabolic control – dyslipidaemia, glucose intolerance and hypothyroidism.

e. Optimium use of steroid-sparing drugs like azathioprine, methotrexate and hydroxychloroquine.

f. Hormone replacement therapy,

g. Supportive measures.

h. Osteoporosis Prophylaxis.

**Table 3: Long-term complications observed in authors series (N=142)**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>17</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>13</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>9</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>8</td>
</tr>
<tr>
<td>Ovarian failure</td>
<td>7</td>
</tr>
<tr>
<td>Retinal toxicity</td>
<td>6</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>2</td>
</tr>
<tr>
<td>Shrinking lung syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

 accounted for 30% of deaths. The mortality rate from CAD in SLE patients is estimated to be nine-fold greater than the predicted population-based studies. Even patients below 35 years have been shown to have severe atherosclerotic narrowing of coronary arteries in autopsy studies. The major predictors of coronary artery disease in SLE patients are age, long duration and dose in excess of 10 mg per day of prednisolone use, hypertension, morbid obesity and hyperlipidemia. In order to prevent these complications rigorous control of blood pressure and lipids is warranted.49 The NECP guidelines for lipid control, especially for the control of high LDL cholesterol should be strictly followed. Disease in organs like kidney may exacerbate the atherosclerotic process indirectly by causing hypertension and hyperlipidemia. Even circulating immune complexes may promote intracellular cholesterol accumulation and act as additional factors.

10. **Phlebothrombosis and pulmonary embolism:** This is observed in the late stage of SLE due to circulating lupus anticoagulant48 and is characterized by swollen limbs. Venous Doppler study will reveal the diagnosis. The risk of pulmonary embolism is high. The elevated D-dimer in blood assay is often used as a screening test for pulmonary thrombo-embolism.

**CHILDHOOD LUPUS**

In a cohort of North Indian patients the outcome of 27 childhood lupus patients was evaluated. Growth retardation was encountered in seven children, steroid induced hypertension in one, amenorrhoea in one and reversible chloroquine eye toxicity in one.50

**Our Observations**

We have followed up 173 patients of SLE patients during the period of 1984-99. Out of these 173 patients 142 patients were followed for 5 years and above; 31 patients were followed for more than 10 years. The age group ranged from 28-62 years (33 males, 109 females). The different late complications observed are shown in Table 3.

**Table 4: Causes of late mortality observed in author’s series (N=142)**

<table>
<thead>
<tr>
<th>Causes</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD</td>
<td>5</td>
</tr>
<tr>
<td>CAD</td>
<td>3</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
</tbody>
</table>

The issue of late complications in SLE patients has become rather important with the prolonged survival of these patients. The major risk factors for such complications include higher age at disease onset, hypertension, associated hyperlipidaemia, diabetes mellitus or hypothyroidism, increasing body mass index, high dose steroid therapy and hyperhomocysteinaemia. In order to detect these complications at the earliest phase of clinical suspicion, sophisticated tests like carotid USG, bone densitometry, MRI of hip joints, pulmonary function tests and myocardial SPECT need to be performed in specific subsets of patients. Early detection of risk factors causing late complications may help the clinicians to readjust therapeutic approaches and to plan prophylactic therapy.

**REFERENCES**


