

Cardiovascular Involvement in Systemic Lupus Erythematosus

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1. Introduction

Cardiovascular involvement in systemic lupus erythematosus (SLE) was first reported by Kaposi in 1872 of cardiac irregularity and dyspnea. In 1924, Libman and Sacks reported verrucous endocarditis but ironically did not recognize the association of verrucous endocarditis with SLE. (Petri, 2004) In the last decade, newly recognized clinical entities have been described with the introduction of very sensitive, non-invasive and semi-invasive cardiac imaging techniques.(Turjel, 2005) With the use of very sensitive methods of cardiovascular investigations, it has been found the prevalence of cardiac involvement to be >50%. (Petri, 2004)

Several autoantibodies such as antiDNA, anti-phospholipid antibodies (apl), antiSSA (Ro antibodies) and antiendothelial cell antibodies present in patients with SLE can mediate cardiac damage. These autoantibodies can directly affect the heart tissue or, alternatively, trigger mechanisms able to cause heart damage for example, apl can contribute to cardiac damage enhancing atherosclerosis phenomena, causing thrombosis of coronary arteries or starting an immune-complex mediated reaction and deposition at the valve level. Consequences of autoantibody damage has been reported in several heart structures such as the valves, myocardium, pericardium, conduction tissues and cardiac arteries in patients suffering from SLE, antiphospholipid syndrome (APS), Sjogrens syndrome and other autoimmune rheumatic diseases(ARD). (Tincani et al, 2006)

Overall improvements in medical care including the availability of antibiotics, antihypertensive, and renal replacement therapy coupled with the judicious use of glucocorticoids, antimalarial and immunosuppressive drugs have led to improved survival of SLE patients in the past 50 years. (Nikpou, 2005) In 1976, Urowitz first described the 'bimodal mortality pattern' of SLE. This observation was based on SLE deaths early in the course of the disease were due to active SLE and use of high dose steroids associated with complications such as infection and sepsis. Later in the disease course (>5 years after diagnosis) deaths were frequently associated with inactive SLE, long duration of prednisolone therapy and myocardial infarction (MI) due to atherosclerotic heart disease. (Urowitz, 1976) Cardiac disease has recently been acknowledged as a primary cause of morbidity and mortality in SLE as well as APS, and numerous factors leading to accelerated

atherosclerosis has been characterized. Though cardiac involvement is a uncommon cause of flare: it can be forgotten unless a full blown cardiac dysfunction or complication is present. In a prospective study of flares, serositis was present in only 7-9% of the flares. (Petri, 1991) With prolongation of life by modern immunosuppressive therapies, heart lesions develop in all patients at sometime during the course of their disease.

The present chapter:

Emphasizes and describes the cardiac involvement in SLE which may involve all three layers of the heart (pericardium, myocardium and the endocardium). Appreciate the early identification and management of these conditions prevents the late life threatening complications and consequences. Recognize the importance of premature atherosclerosis and that it is the major cause for mortality and premature death in lupus patients. Understand the causation is multifactorial: traditional risk factors as well as SLE related risk factors and inflammatory mediators are involved in the pathogenesis. Early identification and treatment of modifiable risk factors in SLE patients are discussed. There have not yet been any published randomized, controlled trials in patients with SLE in respect to CVD risk factor modifications. Thus treatment and management recommendations are based on published guidelines for other populations at high risk for CVD.

2. Pericarditis

2.1 Clinical features

Pericarditis is the most common cardiac manifestation of active lupus, although often it is not evident clinically. Pericarditis can occur at any time during the course of SLE, it tends to be one of the earlier cardiac manifestations, and can even be the first manifestation of lupus. (Brigden, 1960) Pericarditis was the presenting sign of lupus in 4 of 28 patients who ultimately developed it in one series. (Godeau et al. 1981) Pericarditis in SLE presents in the typical way, with precordial pain, usually positional (aggravated by lying down), often with a pleuritic quality, and sometimes with dyspnea. Coexistent pleurisy and/or effusions are common, occurring in 14 of 28 cases in same series. (Godeau et al., 1981) Pericarditis usually appears as an isolated attack or as recurrent episodes, with or without symptoms. Patients may have fever and tachycardia. Friction rubs are rare, perhaps because they are present often for only a few hours and are missed. The "classic" pericardial friction rub has three components, occurring with ventricular contraction, atrial contraction, and at the end of rapid ventricular filling. (Petri, 2004) In a French series, of 28 cases of pericarditis, 23 had pain, 12 had a rub, and 4 required pericardiocentesis because of tamponade. (Godeau et al., 1981) Patients with pericardial effusion (as opposed to thickening) are more likely to have pericardial pain and active lupus elsewhere. (Leung et al, 1990, Cervera et al, 1992) In the study by Cervera et al, only the patients with moderate or severe pericardial effusion had clinical or electrocardiographic evidence of pericarditis. (Cervera et al, 1992) When present, pericardial effusions are usually small and do not cause hemodynamic problems. Pericardial tamponade is rare and has been reported as an initial presentation (Topaloglu, 2006) and even in treated patients. (Shearn, 1959 In a series reported by Rosenbaum, 9 of the 71 patients with pericardial effusion developed pericardial tamponade (21%) of which 5 of the 9 patients required a pericardial window. (Rosenbaum, 2009) Constrictive pericarditis is very rare. Only four cases of constrictive pericarditis have been reported. In two of the four cases constrictive pericarditis developed in spite of corticosteroid therapy. All four known cases have occurred in males. (Petri, 2004)

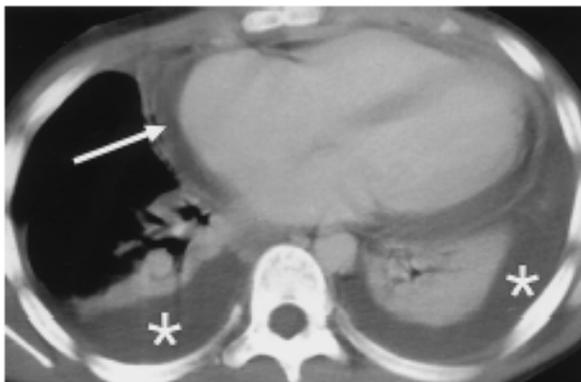


Fig. 1. Serositis in a 13-year-old boy with SLE. Contrast-enhanced CT scan shows bilateral pleural effusions (*), cardiomegaly, and a pericardial effusion (arrow). Bilateral lower lobe atelectasis is also present. (Lalani & Hatfield, 2004) Copyright permission from RSNA

2.2 Diagnosis

If a patient presents for the first time with pericarditis, it is usually impossible to invoke SLE as the cause until appropriate laboratory tests are available suggesting the diagnosis. However, patients with idiopathic pericarditis more often give a history of recent viral infection, and are more often male. In idiopathic pericarditis there is usually a leukocytosis, whereas a finding of leucopenia would suggest SLE. Pericardial friction rubs may be heard in sicker and untreated patients, but are often absent in milder cases, especially those patients already on corticosteroid and/or NSAID treatment. A significant rise in jugular venous pressure is unusual. (Petri, 2004) In one series, most patients showed electrocardiographic evidence of acute or chronic pericarditis. (Brigden et al, 1960) The diagnosis of pericarditis can be confirmed by ECG findings of elevated ST segments and tall T waves (although slight T-wave changes or transient elevation of ST segments are most characteristic), or by cardiac echocardiogram findings of pericardial effusion or thickened pericardium. Serial electrocardiograms may show a progression of changes in pericarditis. Initially, a diffuse elevation of ST segments (without reciprocal ST segment depression) is found. This is followed by a lowering of ST segments back toward baseline and subsequent T-wave inversion. In most cases, T waves then return to normal. (Petri, 2004) Effusions may be accompanied by a drop in voltage. After severe attacks, the T waves may not recover to their original voltage. (Brigden, 1960) In the series of Godeau *et al.*, of 28 cases, 5 had low voltage, 10 had ST changes, and 20 had depolarization changes. (Godeau et al, 1981) Both effusion and thickening are frequent in echocardiogram studies. Most effusions are mild. Echocardiography (two-dimensional echocardiogram and Doppler echocardiography) is the modality of choice in evaluating pericardial disease, because it is both noninvasive and sensitive. However, echocardiography may be an insensitive technique in diagnosing pericarditis when it is not accompanied by effusion or thickening. (Petri, 2004)

2.3 Prevalence

The frequency of pericarditis depends on the modality of diagnosis. Published series of patients find pericarditis in 12–47% of living SLE patients. (Petri, 2004) In general, the

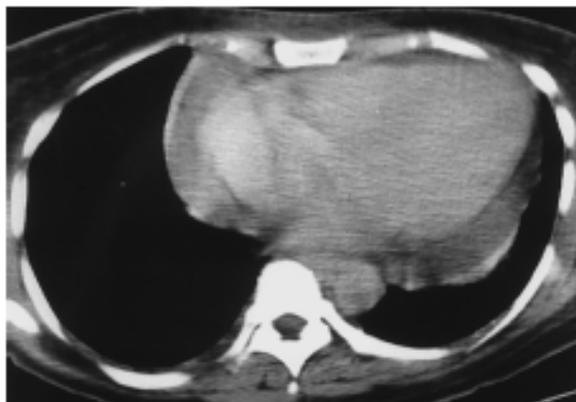


Fig. 2. Lupus pericarditis in a 42-year-old woman. Contrast-enhanced CT scan demonstrates cardiomegaly, a thickened and enhancing pericardium, and a pericardial effusion. . (Lalani & Hatieldl, 2004) Copyright permission from RSNA

echocardiogram is more sensitive than clinical diagnosis, with 19–54% of patients having pericardial effusion or thickening. The echocardiogram is an essential tool in the clinical management of sick patients with cardiac lupus, because clinical diagnosis alone may be faulty. Pericardial abnormalities are the most common echocardiographic finding in SLE patients. (Leung, 1990) However, significant pericardial disease is uncommon, even using echocardiograms, being found in only 7% in one study by Cervera et al. (Cervera et al, 1992) Autopsy studies find a much higher prevalence of pericardial involvement, ranging up to 61–100%. (Petri, 2004)

2.4 Pathology

Pericardial fluid in SLE is usually exudative, the amount of fluid varying from 100 to more than 1000 cc. (Tincani, 2006) White blood counts are in the 30,000 range, primarily neutrophils. Although not helpful in patient management, the fluid may contain anti-DNA and have low complement levels. Complement-fixing material was found in pericardial fluid in patients with SLE, which was felt to be immune complexes. (Petri, 2004) At autopsy, a diffuse or focal fibrinous pericarditis, often with many hematoxylin bodies, with or without effusion, was found. In the series of Brigden *et al.*, the layers of the pericardium were obliterated with occasional deposits of fresh fibrin or effusion. (Brigden, 1960) In another autopsy study, of 11 cases, 6 had acute pericarditis and 5 had chronic obliterative pericarditis (2 of these had pericardiomeastinal adhesions). (Bidani, 1980)

The histopathology in a case of constrictive pericarditis showed fibrosis and mild chronic inflammation, with IgG, IgM, and complement deposition on immunofluorescence. Immunopathogenetic analyses of the pericardium in 2 of 9 patients in an autopsy series demonstrated the vascular deposition of immunoglobulin and complement. (Bidani, 1980) On histopathology, small pericardial blood vessels were surrounded by an infiltrate of lymphocytes, plasma cells, macrophages, and rare polymorphonuclear leukocytes. On immunofluorescence, IgG was present in a predominantly granular pattern around small pericardial vessels. Thus, Bidani and colleagues concluded that immune complex deposition was the cause of pericarditis. (Bidani, 1980)

2.5 Treatment

In early studies, pericarditis usually responded quickly to corticosteroids, with serial chest x-rays showing rapid and radiologic evidence of resorption of fluid.(Brigden,1960) Shearn commented in his review that the "often transient nature of pericarditis makes evaluation of therapy for this condition most difficult.(Shearn, 1959) However, many studies have noted pericardial effusion developing or persisting even with corticosteroid treatment, such as the autopsy study of Kong *et al.*, in which 11 of 12 patients with pericardial effusion had taken corticosteroids.(Kong *et al.*,1962) Occasionally patients progressed to the point of tamponade.(Rosenbaum, 2009) Nonsteroidal anti-inflammatory drugs are helpful for mild cases of pericarditis. Patients presenting with pericardial tamponade may necessitate pericardiocentesis. Refractory cases of large pericardial effusions may benefit from a pericardial window. (Rosenbaum, 2009)

3. Myocarditis

3.1 Clinical features

Myocarditis, as recognized clinically, is rare in SLE. The clinical detection of myocarditis ranges from 3 to 15%, although it appears to be much more common in autopsy studies suggesting the largely subclinical nature of the myocardial pathology. Patients may present in florid congestive heart failure, or more subacutely with tachycardia and dyspnea. Myocardial abnormalities were found in 20% of patients using echocardiograms, but only one patient with an echocardiographic pattern of myocarditis developed myocardial dysfunction clinically.(Cervera, 1992)

Even autopsy studies have shown that myocarditis usually does not lead to cardiac dilatation.(Griffith & Vural, 1951) Brigden *et al.* had no patient in whom congestive heart failure was attributed solely to myocarditis.(Brigden *et al.*, 1960) Shearn had only one patient with heart failure attributable to myocarditis.(Shearn,1959)

However, other series have found myocarditis as a cause of congestive heart failure. (Petri, 2004) Harvey *et al* found that myocarditis was the cause of heart failure in 8 of their 9 patients. (Petri, 2004) Hejtmancik *et al.* found myocarditis to be the major cause in 6 of their 10 cases. (Hejtmancik *et al.*, 1964). Kong *et al.* had 17 patients with cardiomegaly; at autopsy, 15 had myocarditis but of varying degrees of severity.(Kong *et al.*,1962)

The differential diagnosis of congestive heart failure in SLE would include lupus myocarditis, viral myocarditis, toxic myocarditis due to use of antimalarial drugs, anemia, renal failure, pulmonary disease, atherosclerotic heart disease, coronary arteritis, valvular disease, and hypertension.

3.2 Diagnosis

The clinical recognition of myocarditis can easily be missed. In most cases, the patient who had a hematologic and renal flare was not recognized to have myocarditis as well until they presented in congestive heart failure. Myocarditis should be considered in patients with tachycardia not due to fever, in patients with a third heart sound (S3), in patients with abnormal ECGs, in those with new murmurs or conduction disturbances, and in those with congestive heart failure. (Shearn, 1959) Brigden *et al.* suggested that prolongation of the conduction time of either P-R, QRS, or Q-T interval would have been evidence of myocarditis (in the absence of another cause of ventricular hypertrophy), but that they did not encounter these ECG changes in their series.(Brigden, 1960)

Hejtmancik *et al.* made a clinical diagnosis of myocarditis in 21% of their patients (after first excluding hypertension and coronary artery disease), based on (1) cardiac enlargement, (2) ventricular gallop, and (3) electrocardiographic abnormalities.(Hejtmancik et al, 1964) Kong *et al.* found myocarditis at autopsy in 15 of their 16 patients with gallop rhythm.(Kong et al, 1962).The diagnosis of myocarditis can be supported by the finding of global hypokinesia on cardiac echocardiogram and may be confirmed by right ventricular endomyocardial biopsy.(Petri,2004) Although echocardiography cannot diagnose myocarditis with certainty, global hypokinesia, in the absence of other known causes, is strongly suggestive.(Busteed et al, 2004) Other investigations that may help to diagnose myocarditis include a gallium scan¹⁸ and magnetic resonance imaging (MRI).(Saremi et al, 2007) Nuclear medicine scans rely on labeling of anti myosin antibodies with radiopharmaceuticals, and may not be available in all clinical settings. Different MRI techniques may support the diagnosis of myocarditis. Contrast enhancement of the myocardium in the setting of acute myocyte membrane rupture results in greater passive diffusion of contrast into the affected intracellular space. A midwall myocardial hyperenhancement pattern is the most frequent finding in both acute and chronic myocarditis, while a subepicardial distribution of lesions is reported only in patients with acute myocarditis.(Saremi et al,2007) However, it is important to note that MRI alone cannot differentiate viral myocarditis from other causes of acute dilated cardiomyopathy. A biopsy is not required in many cases of lupus myocarditis, as the sensitivity and specificity are unknown; but can be useful in some patients to confirm the clinical diagnosis, determine the severity of myocardial involvement, and distinguish this disorder from other causes of myocardial disease like drug induced etc.(Wijetunga & Rockson, 2002) New-onset heart failure of less than 6 days' duration associated with hemodynamic compromise is an American Heart Association/American College of Cardiology/European Society of Cardiology class I indication for endomyocardial biopsy.(Cooper et al,2007)

3.3 Prevalence

In large series of patients, the clinical diagnosis of myocarditis has been made in up to 21%. (Petri, 2004) Autopsy studies, mainly done in the 1950s and 1960s, frequently found myocarditis. More recent postmortem studies,(Bindani, 1980) reflecting the era of corticosteroid treatment, found much lower frequencies, from 0 to 8%. Echocardiographic studies cannot definitively diagnose myocarditis, but global hypokinesia, in the absence of other known causes, is strongly suggestive. (Appenzeller, 2011) Large echo series have found frequencies of global hypokinesia between 5 and 20%. However, segmental areas of hypokinesia on echocardiogram can also be indicative of myocarditis. Newer imaging modalities, such as magnetic resonance, are largely unstudied. (Appenzeller, 2011)

3.4 Pathology

A common misperception is that myocarditis in SLE is a myositis. CPK levels are usually normal.(Petri, 2004) In fact, only one study found any association with myositis elsewhere.(Borenstein et al, 1978) Myocarditis in SLE is a complicated process, with arteritis or arteriopathy, not primary disease of the myocardial fibers, playing a major role. Kong *et al.* found pathologic evidence of myocarditis (fibrinoid and collagenous degeneration, interstitial edema, necrosis, and/or cellular infiltration) in 15 of 30 autopsies. (Kong et al, 1962) The cellular infiltrates of myocarditis consist of foci of interstitial plasma cells and

lymphocytes. Immunofluorescence studies confirm that the etiopathogenesis is vascular. In one study, most of the immune deposits were present in the walls of blood vessels of the myocardium.(Bidani, 1980) Immunofluorescence studies of endomyocardial biopsies reveal perivascular deposits of IgG and vascular deposits of C3.(Appenzeller, 2011) A rare and aggressive form is giant cell myocarditis, which is associated with extensive myocytes necrosis, a mixed dense lymphoplasmacytic infiltration, numerous multinucleated giant cells and degranulated eosinophils, leads to rapidly developing progressive congestive heart failure and arrhythmias.(Chung et al, 2005; Martorell et al, 2008) Antimalarial-related myocarditis is often associated with skeletal muscle involvement showing curvilinear and myeloid bodies.(Nord et al,2004)

3.5 Treatment

Myocarditis that comes to clinical attention is usually an urgent situation. Treatment with high-dose intravenous methylprednisolone (such as the "pulse" regimen, 1000 mg daily for 3 days), followed by high dose IV or oral corticosteroid maintenance therapy, is indicated. Intravenous "pulse" cyclophosphamide is added in refractory cases and patients with heart failure. Initial six cycle of monthly pulses of cyclophosphamide 750mg/m², followed by a repeated cycle if LVEF has not completely normalized, is relatively well tolerated and effective. (Van der Laan Baalbergen et al, 2009) Intravenous immunoglobulin's have been used in one or two case reports with some success.(Sherer et al, 1999)

Supportive therapy for congestive heart failure, including diuresis, digoxin, and afterload reduction (such as with angiotensin converting enzyme (ACE) inhibitors) may be necessary. Anticoagulation should be considered in those patients who have progressed to the stage of cardiomyopathy. Efficacy of therapy can be assessed by serial echocardiographic studies.

One potential therapeutic option in advanced stages of heart failure regardless of the source is cardiac resynchronization therapy (CRT). There have been several reports illustrating the successful use of cardiac resynchronization in patients with SLE and resistant cardiomyopathy. (Reza et al, 2011) Mortality is higher in giant cell myocarditis than other forms of myocarditis. (Cooper et al, 1997) Cardiac transplantation is an option in refractory cases. (Reza et al, 2011)

4. Valvular disease

4.1 Clinical features

Verrucous endocarditis can affect valve leaflets, papillary muscles, and the mural endocardium, as initially described by Libman and Sacks. However, Libman and Sacks and Gross found the tricuspid valve involved most often, whereas more recent studies have found the mitral valve (followed by aortic) to be most affected.(Petri, 2004) In the corticosteroid era, valvular vegetations are found less frequently. Shearn found that none of 11 patients who received corticosteroids had verrucous endocarditis, but 4 patients, who died before corticosteroid therapy was available, did. (Shaern, 1959) In their landmark autopsy study, Bulkley and Roberts also commented on the rarity of vegetations in corticosteroid treated patients. (Bulkley & Roberts, 1975) Occasionally, the presentation may be fulminant, with congestive heart failure due to mitral regurgitation, or brain emboli secondary to valvular vegetations. Verrucous endocarditis (vegetations, "Libman- Sacks") affects the mitral valve most frequently, followed by the aortic valve. (Petri, 2004)



Fig. 3. Libman Sacks Endocarditis.

The presence of vegetations predisposes patients to bacterial endocarditis. (Brigden et al, 1960) Although verrucous endocarditis can produce both systolic and diastolic murmurs, these are rarely of sufficient hemodynamic importance to cause congestive heart failure. There is virtually no correlation between the presence of verrucous endocarditis and cardiac murmurs. Shearn found that systolic murmurs occurred in 70% of SLE patients. (Shearn, 1959) Most murmurs were low intensity, and were heard loudest (47%) at the apex. Because murmurs were also associated with fever, infection, tachycardia, and anemia, the differential diagnosis of a new murmur was complex.

Diastolic murmurs occur in only 4% of SLE patients. (Petri, 2004) The differential diagnosis of diastolic murmurs in SLE includes rheumatic or congenital heart disease, bacterial endocarditis, Libman-Sacks endocarditis, and left ventricular dilatation. In general, even when the valvular vegetations of Libman-Sacks endocarditis are large, they do not involve the line of closure, and therefore should not deform the valve. Even involvement of the chordae tendineae should not be sufficient to distort the valve. There are several documented cases, however, in which Libman-Sacks endocarditis appeared to be the only explanation for a diastolic murmur. (Petri, 2004) Two of the four patients with Libman-Sacks endocarditis in Shearn's series had a diastolic murmur suggestive of mitral stenosis. However, diastolic murmurs were also heard in two patients without Libman-Sacks endocarditis. (Shearn, 1959) It is rare for valvular disease in SLE to be clinically significant. In a series of 421 patients, only 1 to 2% had significant morbidity or mortality. Of the 14 cases with available pathology, only 6 had evidence of SLE valvulopathy, either verrucous vegetations or valvulitis with necrosis and vasculitis. (Straaton et al, 1988)

4.2 Diagnosis

Transesophageal echocardiogram is the modality of choice in terms of sensitivity in detecting valvular disease due to either lupus or anti-phospholipid antibody syndrome.

(Petri, 2004) Most previous series used M-mode echocardiography or two-dimensional Doppler echocardiography and are not completely comparable. Patients with new murmurs or with valvular abnormalities on echocardiogram should have blood cultures to rule out bacterial endocarditis.

4.3 Prevalence

The prevalence of valvular disease in SLE is very high by echocardiography accounting for 54% of the patients. (Maksimowicz-McKinnon & Mandell, 2004) Valvular disease, for the most part, however, is mild and asymptomatic.

4.4 Pathology

Valvular disease occurs predominantly as vegetations (what was termed Libman-Sacks endocarditis in the past), or thickening (that can present as either a regurgitant or stenotic lesion). The mitral valve is affected most often, followed by the aortic valve. Mitral and aortic regurgitation are the most common findings, with stenotic lesions being very rare. Aortic cup sclerosis has been identified as common lesion. The typical valvular and mural endocarditis lesions, which are verrucous, occur as single vegetation or as mulberry-like clusters. When occurring on valves, the vegetations are often on the ventricular surface, near, but not distorting, the line of closure. (Shapiro et al, 1977) The original histologic description of Libman-Sacks endocarditis emphasized the multiplication of endothelial cells, proliferation of Anitschow myocytes, and infiltration of mononuclear cells in the valve ring and valve base, especially the valve pocket. Aggregations of hemosiderin were frequent, along with some fibrosis. Cells underwent karyolysis to form hematoxylin bodies. The mural endothelium was affected, especially near the mitral valve. (Brigden et al, 1960) Histologic studies showed three distinct zones, an outer exudative layer of fibrin, nuclear debris, and hematoxylin-stained bodies; a middle organizing layer of proliferation of capillaries and fibroblasts, and an inner layer of neovascularization. Immunofluorescence showed immunoglobulin and complement deposition in the walls of small junctional vessels in the inner zone of neovascularization, suggesting that circulating immune complexes were critical in the development of the vegetations. (Shapiro et al, 1977) Bidani *et al.* found immunoglobulins and complement deposition in the valve stroma and vegetations in one patient with Libman-Sacks endocarditis. (Bidani, 1980) It is not clear whether Libman-Sacks endocarditis evolves into the valvular thickening that is the second important form of SLE valvulopathy. In modern series, valvular thickening is found more commonly than vegetations (Leung, 1990). Galve *et al.* found that patients with Libman-Sacks endocarditis were younger, had shorter disease duration, and had received less corticosteroid therapy than those with thickened valves. (Galve et al, 1988) The patients with valvular thickening were more likely to have stenotic or regurgitant lesions and to require valve replacement. (Galve et al, 1988) Some authors have expressed concern that corticosteroid treatment might increase the chance that a valve would develop thickening. Changes in valve thickening can occur over time, with valve thickening resolving or new valve thickening appearing. Studies are conflicting on the role of antiphospholipid antibodies playing in the development of the vegetations of Libman-Sacks endocarditis. Valvulopathy is common in the primary anti-phospholipid antibody syndrome, usually found in about a third of patients in large series. (Khamashta et al, 1990) Thrombus formation, usually on the mitral valve, can be massive and require valve replacement.

Mitral and/or aortic valve thrombus (or vegetations) can also be a precipitant of embolic strokes. In SLE patients, some series have shown significantly more valvulopathy in those with anticardiolipin antibody.(Khamashta et al,1990) In patients with the secondary form of anti-phospholipid antibody syndrome and valvulopathy, there is deposition of immunoglobulin and complement, but in addition there is binding of anticardiolipin antibody.(Petri, 2004)

4.5 Treatment

Systemic lupus erythematosus patients with large, sterile vegetations should be anticoagulated to lessen embolic complications. High-dose corticosteroids for 4 to 6 weeks are used to shrunken the vegetations, but this approach is controversial.(Neshet et al, 1997) Some studies have suggested that corticosteroid treatment may contribute to ultimate valve thickening, but this is unproven. In the presence of significant regurgitation, even in the absence of nodules, there is a high risk of bacterial endocarditis particularly in the setting of jet lesions and warrant antibiotic prophylaxis. (Roman & Salmon, 2007)

5. Arrhythmia and conduction defects

5.1 Clinical features

Many autoimmune diseases including systemic lupus erythematosus have a high incidence of autonomic nervous system dysfunction, especially those of cardiac origin. Conduction disturbances and arrhythmias occur in about 10% of patients with SLE. (Mandell, 1987) Conduction defects include AV block, BBB and complete heart block, which is rarely seen in adults. While the most common arrhythmic manifestation include sinus tachycardia, atrial fibrillation, atrial ectopic beat and rarely ventricular arrhythmias. (Eisen et al, 2009) Recently, other anti-SSA/Ro-associated cardiac manifestations have been described in children born to anti-SSA/Ro positive mothers. These include transient fetal first-degree heart block, QTc prolongation, sinus bradycardia, late onset cardiomyopathy, endocardial fibroelastosis and cardiac malformations. Anti-SSA/Ro antibodies are usually not pathogenic to the adult heart, but recently QTc prolongation has been reported in adult lupus patients as well.(Costedoat-Chalumeau et al, 2005)

Sinus tachycardia is the most common cardiac abnormality seen among SLE patients. It is present in about 50% of cases (Hejmancik et al, 1964) and it could be the only manifestation, also it can be correlated to the disease activity. (Guzman et al, 1994) Arrhythmia and conduction defects in SLE patients may be found incidentally or during disease flare, and usually develop with coexisting cardiac manifestation (such as pericarditis, myocarditis and coronary heart disease though, arrhythmia may be the first manifestation of SLE . (Cardoso et al, 2000)Patients with SLE may have prolonged Q-T interval, and this can be a predictor of cardiovascular morbidity and mortality. (Okin et al, 2000)

5.2 Pathogenesis

SLE can lead to arrhythmias and conduction disturbances either as a consequence of pericarditis and myocarditis through direct injury of the conduction system of the heart by inflammatory processes.(Eisen et al, 2009)Supraventricular arrhythmias are usually transient and recedes as soon as the disease is controlled and treated.(Mandell, 1987) They can also be due to myocardial fibrosis as a consequence of occlusive diseases, (ischemia) due to

vasculitis and atherosclerosis involvement (Eisen, 2009). These mechanisms will result in collagen deposits that accumulate within nodes, causing fibrosis and focal degeneration of the conduction system. (Barati et al, 1975) Autopsy studies have found arteritis of the sinus node, vascular occlusion, vasculopathy, and fibroblastic replacement of the sinoatrial and atrioventricular nodes. (Barati et al, 1975) Q-T interval prolongation is hypothesized to be due to the subclinical atherosclerosis that is known to be augmented in SLE patients, and thus, it can be a marker of silent undetected atherosclerotic vascular disease in SLE patients. (Cardoso et al, 2005) In addition to Q-T interval prolongation, refractory ventricular arrhythmias could be associated with chronic hydroxychloroquine therapy for SLE. (Chen et al, 2006)

5.3 Management

Diagnosis of arrhythmia and conduction defects is by electrocardiograms that are performed usually in patients with an active disease during hospitalization. Those who have had arrhythmias or conduction abnormalities need continuous ECG monitoring. (Petri, 2004) The life-threatening conduction defects are treated with permanent pacemaker, while the supra-ventricular arrhythmias (unexplained sinus tachycardia) can be controlled with corticosteroids. (Costedoat-Chalumeau, 2005; Guzman et al, 1994)

6. SLE hypertension

6.1 Prevalence

Hypertension has a high prevalence among SLE patients ranging from (35 to 74%) according to different studies (Doria et al, 2003; Petri, 2000) and it is considered as a major risk factor for the progression of renal, vascular and cardiovascular diseases. In addition, it's a major risk factor of severe ischemic stroke, thus reflecting the need of regular assessment and strict blood pressure control among SLE patients. (Mikdashi, 2007)

6.2 Pathophysiology

The pathogenesis of hypertension in SLE is multifactorial where alteration of renal function plays a central role; other mechanisms can contribute such as renin-angiotensin-aldosterone system (RAS), endothelin, oxidative stress, sex steroids and metabolic changes. Involvement of the kidneys in the course of SLE is common and impaired renal function plays a role in development of hypertension by alteration in the renal hemodynamic that leads to reduction in glomerular filtration rate (GFR) and increase in BUN and plasma creatinine levels. (Nakaro et al, 1998) Renal tubular lesions are prevalent in SLE patients, (Daniel et al, 2001) as well as glomerular injury in the form of glomerulonephritis contributes to SLE hypertension that is clinically indicated by the presence of urinary protein in SLE patients. (Ryan, 2009) SLE is usually associated with impaired endothelial function as demonstrated by the high risk of atherosclerosis, and this may also have a role in development of SLE hypertension. (Ryan, 2009) The Renin-Angiotensin-Aldosterone System (RAS) is activated in SLE (Herlitz et al, 1984) on basis of effectiveness of BP control with ACE inhibitors and evidence of increased renin, which thus can play a role in developing SLE hypertension. (Ryan, 2009)

Endothelin-1 (ET-1) plays a role in the pathophysiology of hypertension through its potent renal vasoconstriction and its ability to cause water and sodium retention. (Miyachi &

Masaki, 1999) Evidence suggests that ET-1 could have role in the progression of SLE and SLE hypertension as the level of ET-1 are found to be increased in SLE.(Julkunen et al, 1991) Activated RAS and increased ET 1 levels in SLE could lead to the generation of oxidative stress (Ryan, 2007) that is suggested to be important in pathogenesis of SLE(Alves & Grima, 2003) and it is recognized as a promoter of hypertension through mechanisms such as vascular dysfunction , renal injury and increase sodium reabsorption.(Manning et al, 2003) In addition , metabolic factors can contribute in the pathophysiology of hypertension in SLE and these include: Leptin, which is found to be increased, insulin resistance, and obesity.(Gehi et al 2003) Inflammatory cytokines (IL-6, TNF α , and CRP) correlate in the mechanism of hypertension. (Bastista, et al, 2005)As these cytokines are increased in SLE, they are suggested to be involved in SLE hypertension through mechanisms such as, promotion of renal vascular endothelial dysfunction, generation of oxidative stress and progression of insulin resistance. (Garcia-Gonzalez et al, 2002)

6.3 Management

(Discussed in the section of management of traditional risk factors 8.6.1.)

7. Coronary arteritis

7.1 Clinical features

Coronary arteritis is extremely rare in SLE. In some cases, it has been found at autopsy, with no clinical correlate during life. The most common clinical presentation is angina and/or myocardial infarction, in a child or young adult who does not have a long history of corticosteroid therapy. (Petri, 2004) There is no clear correlation with extracardiac disease activity, although it has been present in some case. (Korkmaz & Cansu, 2007) Three of eight SLE patients who had a coronary artery aneurysm had no physical or laboratory evidence of active SLE. (Wilson et al, 1992) Aortic aneurysms can also occur in SLE. (Ohara et al, 2000)

7.2 Diagnosis

It is often difficult to distinguish coronary arteritis from accelerated atherosclerosis. Serial coronary angiography has been proposed as the most useful diagnostic modality. Arteritis is suggested when coronary aneurysms are found, if there are smooth focal lesions, or if there are rapidly developing stenoses.(Petri, 2004) However, Wilson *et al.* described a patient with rapidly progressive coronary artery occlusions in whom only advanced atherosclerosis was found at autopsy. (Wilson et al, 1992) Thrombosis or spasm can further confuse the interpretation of coronary angiograms. (Korkmaz & Consu, 2007)

7.3 Prevalence

There are few studies that allow any estimate of the prevalence of coronary arteritis. (Petri, 2004) In one study in the 1960s, 6 of 16 patients were found to have arteritis at autopsy. (Hejmancik et al, 1964)

The cases identified have a predilection for pediatric patients or very young adults, with rare exceptions. Unfortunately, where follow is given, the outcome is usually death.

7.4 Pathology

Histopathology demonstrates transmural vasculitis with both lymphocytic and neutrophilic infiltration of a thrombus. (Korkmaz & Consu, 2007)Immunofluorescence studies

demonstrate immunoglobulin and complement deposition in coronary arteritis. (Korbet et al, 1984)

7.5 Treatment

The differentiation of coronary arteritis from atherosclerosis is essential for appropriate management. Coronary artery bypasses surgery, angioplasty, or stent placement would be considered in patients with severe atherosclerotic disease, but would be contraindicated in patients with coronary arteritis. Case reports suggest that corticosteroid therapy can have rapid benefit in patients with coronary arteritis. Corticosteroid therapy resulted in relief of angina and angiographic improvement. (Kozkmaz & Cansu, 2007) Not all patients with coronary arteritis do well on corticosteroids, however Heibel *et al.* describe a patient with coronary arteritis who was treated with prednisone and cyclophosphamide, but had new myocardial damage after starting therapy. (Heibel et al, 1976) Angina did not resolve for 3 weeks. (Heibel et al, 1976)

8. Premature atherosclerosis and systemic lupus erythematosus

8.1 Background-premature atherosclerosis and systemic lupus erythematosus

Despite improved life expectancy, patients with systemic lupus erythematosus (SLE) are still at considerable risk for premature death.(Galdman & Urowitz, 2002) This has been related to the high frequency of vascular events (VE) in young to middle-aged SLE patients, in whom atherosclerosis develops at an accelerated pace. (Bruce et al, 2003) Although general, modifiable risk factors for atherosclerosis are also relevant in SLE, they cannot fully explain the increased rate of atheroma formation. (Esdaile et al, 2001) SLE is the prototype of the immune complex mediated systemic inflammatory disorders, and inflammation has a central place in the pathogenesis and growth of atherosclerotic plaques. (Thomas et al, 2002; Becker & Nossent, 2009) Reducing the level of inflammatory activity in SLE would, thus, be a rational way to decrease this VE risk. (Pans-Estel et al, 2009)

Premature atherosclerosis (ATH) has been recognized as a major comorbid condition in systemic lupus erythematosus (SLE). Women with SLE in the 35–44year old age group have an estimated 50-fold increased risk of myocardial infarction (MI) compared to age and sex-matched controls. (Manzi, 1997) Women with SLE also have an increased incidence of subclinical atherosclerosis; in a study using carotid ultrasounds, a 37.1% prevalence of carotid atherosclerosis was found in lupus patients compared to 15.2% of controls.(Szeknanecz & Shoenfeld, 2006) Although traditional risk factors as defined by the Framingham studies (hypertension, hypercholesterolemia, diabetes mellitus, older age, and postmenopausal status) are important in increasing risk for ATH in SLE, they do not adequately explain the increase in cardiovascular disease. In a Canadian cohort, after controlling traditional risk factors, the relative risk attributed to SLE for myocardial infarction (MI) was 10.1 and for stroke 7.9 (Esdaile et al, 2001) It has increasingly become evident that inflammation and immune mechanisms play an important role in the pathogenesis of atherosclerosis in SLE. For many years, the development of atherosclerosis in the general population was regarded as a passive accumulation of lipids in the vessel wall. Recently, however, it has been realized that inflammation plays a role not only in the development of the atherosclerotic lesion but also in the acute rupture of plaques that occurs during acute myocardial ischemic events. (Von Felt, 2008)

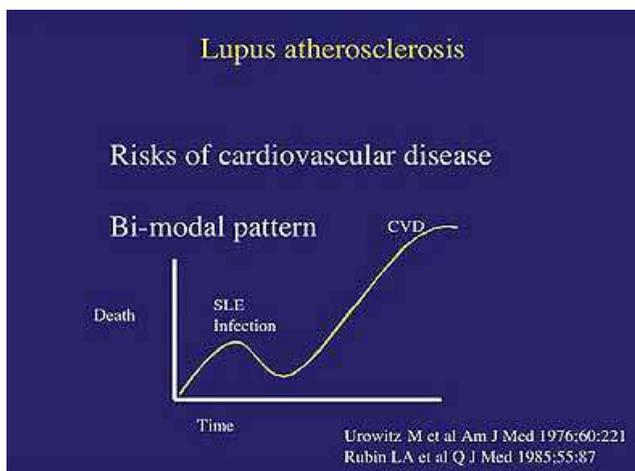


Fig. 4. The bimodal pattern of mortality in SLE patients. (Urowitz et al, 1976; Rubin et al, 1985) Copyright permission from Elsevier

8.2 Etiology of premature CVD in SLE

The pathogenesis of premature atherosclerosis in lupus is multifactorial and includes traditional CV risk factors, lupus -related factors and inflammatory risk factors. Box 1

8.2.1 The role of inflammation in the pathogenesis of atherosclerosis

The recruitment of inflammatory cells to the arterial wall Atherosclerotic lesions begin with the recruitment of inflammatory cells such as monocytes and T cells to the endothelial wall. First, the vascular endothelial cells are stimulated to express leukocyte adhesion molecules, including E-selectin, vascular cell adhesion molecule-1(VCAM-1), and intercellular adhesion molecule-1 (ICAM-1). (Hansson, 2001) These cell-surface proteins are upregulated during periods of inflammation. The expression of adhesion molecules can be induced by proinflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1), which upregulate leukocyte adhesion molecules. (Hansson, 2001) VCAM-1 is also induced when endothelial cells are exposed to other inflammatory signals, such as the lipopolysaccharides of Gram-negative bacteria, lysophosphatidylcholine (LPC), and oxidized phospholipids such as oxidized low density lipoprotein (OxLDL). High-density lipoproteins (HDLs) inhibit the expression of adhesion molecules. (Calabresi et al, 1997) After leukocytes adhere to the cell surface, they migrate through the endothelium and into the intima. (Hansson, 2001) This transmigration is influenced by several factors: first, several chemotactic proteins such as monocyte chemoattractant protein-1 (MCP-1) are produced by the endothelial and smooth cell layers. The expression of MCP-1 in smooth muscle cells and endothelial cells can be upregulated by cytokines such as TNF- α , IL-1 and by OxLDL. (Hansson, 2001) Conversely, normal HDLs inhibit the expression of MCP-1. The importance of MCP-1 in the development of the atherosclerotic plaque is emphasized by the fact that elevated circulating levels of MCP-1 are positively related to increased carotid artery IMT in humans. (Larson et al, 2005)

Traditional risk factors

- Age
- Smoking
- Hypertension
- Hypercholesterolemia
- Diabetes mellitus
- Family history

Novel cardiovascular disease risk factors

- Cytokines (TNF- α , IFN- α , IL-6 and low IL-10)
- Endothelial (sVCAM-1, VEGF, Ang-2, apoptosis of circulating angiogenic cells/ endothelial progenitor cells and low annexin V binding)
- Elevated C-reactive protein
- Elevated homocysteine
- Metabolic syndrome/insulin resistance

Lupus-specific variables

- Corticosteroids
- SLE disease activity and SLE disease damage
- Antiphospholipid antibodies
- Anti-oxLDL antibodies, reduced antiphosphorylcholine antibodies
- Proinflammatory HDLs
- Lupus dyslipoproteinemia (high VLDL, high triglyceride, low HDL, high lipoprotein A); decreased lipoprotein lipase activity
- Renal disease

Ang-2: Angiopoietin-2; HDL: High-density lipoprotein; oxLDL: Oxidized low-density lipoprotein; SLE: Systemic lupus erythematosus; sVCAM: Soluble vascular cellular adhesion molecule; VLDL: Very low-density lipoprotein.

(Skamra & Ramsey-Goldman, 2010)

Box 1. Risk factors for cardiovascular disease in systemic lupus erythematosus (Elliot JR, Mansi S, 2009. Copyright permission from Elsevier)

8.2.2 Low-density lipoproteins and the development of foam cells

Next, low-density lipoproteins (LDLs) are transported into artery walls, where they become trapped and bound in the extracellular matrix of the subendothelial space.(McMahon & Hahn, 2007) These trapped LDLs are then seeded with reactive oxygen species (ROS) produced by nearby artery wall cells, resulting in the formation of proinflammatory-oxidized LDL . When endothelial cells are exposed to these proinflammatory OxLDL, they release cytokines such as MCP-1, M-CSF, and GRO, resulting in monocyte binding, chemotaxis, and differentiation into macrophages. (Nawab et al, 2000)

The OxLDLs are phagocytized by infiltrating monocytes/ macrophages, which then become the foam cells around which atherosclerotic lesions are built. Elevated levels of circulating OxLDL are strongly associated with documented coronary artery disease in the general population.(Tsimikas et al, 2005) Elevated levels of circulating OxLDL have also been described in SLE patients, especially in those with a history of cardiovascular disease.(Frostegard et al, 2005)

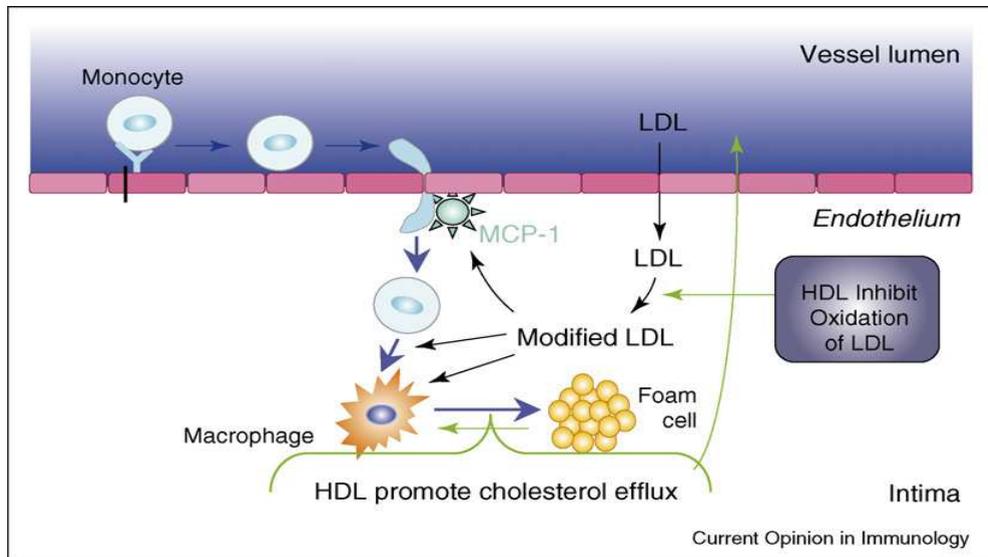


Fig. 5. The interplay of LDL, HDL, and OxLDL with endothelial activation, monocyte migration, foam cell formation, and reverse cholesterol transport. (Macmohan M, Hahn BV, 2007. Copyright permission from Elsevier)

Next, monocytes and T cells infiltrate the margin of the plaque formed by foam cells, and muscle cells from the media of the artery are stimulated to grow. These muscle cells encroach on the lumen of the vessel and ultimately lead to fibrosis, which renders the plaques brittle. The occlusion that results in MI can occur when one of these plaques ruptures, or when platelets aggregate in the narrowed area of the artery. (McMahon & Hahn, 2007)

8.2.3 Normal HDL clears OxLDL from the endothelium: Abnormal proinflammatory HDL associate with accelerated atherosclerosis

There are many mechanisms designed to clear OxLDL from the subendothelial space, including macrophage engulfment using scavenger receptors, and enhanced reverse cholesterol transport mediated by lipoprotein transporters in HDL. (McMahon & Hahn, 2007) In addition to reverse cholesterol transport, HDL removes reactive oxygen species from LDL (via anti-oxidant enzymes in the HDL, such as paroxonase), thus preventing the formation of OxLDL and the subsequent recruitment of inflammatory mediators. (Nawab et al, 2000a, Nawab et al, 2004b)

Thus, although quantities of HDL partially determine atherosclerotic risk (low levels are associated with increased risk), HDL function is equally significant. (Barter et al, 2004) During the acute phase response HDL can be converted from their usual anti-inflammatory state to proinflammatory, and can actually cause increased oxidation of LDL. This acute phase response can also become chronic, and may be a mechanism for HDL dysfunction in SLE. It has been found that HDL function is abnormal in many women with SLE, 45% of women with SLE, compared to 20% of rheumatoid arthritis patients and 4% of controls, had proinflammatory HDL (piHDL) that was not only unable to prevent oxidation of LDL but caused increased levels of oxidation. (McMahon et al, 2006a) McMahon et al reported 86% of patients with SLE who had plaque on carotid ultrasound had piHDL, compared to 39% who do not have plaque ($p < 0.0001$). (McMahon et al, 2006b) This suggests that detecting piHDL may identify SLE patients at high risk for clinical atherosclerosis. The interplay of LDL, HDL, and OxLDL with endothelial activation, monocyte migration, foam cell formation, and reverse cholesterol transport is illustrated in Figure 9.

8.3 Traditional risk factors

Over the past 15 years, traditional CV risk factors have been described in patients with SLE. Patients from several large lupus cohorts have been reported to have a greater total number of Framingham study and other traditional risk factors, including hypertension, diabetes, dyslipidaemia, tobacco use and sedentary lifestyle than matched control subjects. (Asanuma et al, 2003) Others have discovered a greater occurrence of both insulin resistance and metabolic syndrome. The Toronto Lupus Cohort also reported that SLE patients with CV events have a greater total number of traditional CV risk factors than lupus patients without events. (Bruce et al, 2003) Premature menopause is commonly seen in lupus patients. Compared with age-matched controls, women with lupus are more likely to be post-menopausal (38% vs. 19%) and reach menopause 4 years earlier. (Urowitz et al, 2007) These conventional risk factors of CVD are also associated with sub-clinical measures of atherosclerosis in SLE patients. Older age, hypertension, dyslipidaemia and diabetes are associated with the presence of carotid plaque. Finally, both hypertension and dyslipidaemia are independently predictive of CV events (MI and stroke) in SLE patients. (Elliott et al, 2008)

8.4 Dyslipidaemia in SLE

An atherogenic lipid profile has been described in SLE patients with elevated total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and lipoprotein(a) [Lp(a)] concentrations, as well as decreased high-density lipoprotein (HDL) cholesterol levels. (Borba et al, 1994) Patients with lupus may also have altered HDL function. HDL cholesterol is normally an anti-inflammatory molecule that prevents the formation of oxidised LDL (ox-LDL) and foam cells that lead to plaque formation in the vasculature. A pro-inflammatory HDL (piHDL) is less able to prevent oxidation of LDL. piHDL was found in greater frequency in lupus patients with CVD than in those without known coronary disease. (Batuca et al, 2007) Additionally, paraoxonase 1 (PON1) is an anti-oxidant component of HDL that inhibits oxidation of lipoproteins and breaks down ox-LDL. In SLE, PON1 activity is altered, and significant reductions of PON1 are associated with both CV and cerebrovascular events. (Tripi et al, 2006) One possible mechanism for the reduced PON activity seen in SLE may be due to auto-antibody

production. In a study by Batuca et al., patients with SLE were noted to have higher titres of antibodies to HDL and apolipoprotein A-1 (a lipoprotein associated with HDL) than healthy controls. (Batuca et al, 2007) PON activity was inversely correlated with the levels of antibodies to apolipoprotein A-1.

8.5 Lupus-related risk factors

Traditional risk factors alone do not fully explain the increased risk of CVD in lupus patients. Esdaile and colleagues reported a 10-fold relative risk of non-fatal MI and 17-fold relative risk of death from CHD, even after controlling for Framingham study risk factors. (Esdaile et al, 2001) These findings suggest that factors related to lupus itself, as well as its therapy, may be independent risk factors for CVD.

8.5.1 Disease activity

Ongoing inflammatory SLE disease activity is associated with CV risk. (Manzi et al 1997, Roman et al, 2003) A six-point increase in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score over 1 year correlated with a 5% increase in a 2-year CV risk. (Karp et al, 2008) This same increase in SLEDAI score was associated with increases of 3.4 mmHg in systolic blood pressure, 1 mg/dl in glucose and 11.6 mg/dl in TG as well as a 2.3- mg/dl decrease in HDL cholesterol. In the study performed by Roman and colleagues, the diagnosis of SLE itself, a longer duration of disease and greater disease damage (measured by SLICC-Damage Index [SLICC-DI]) were independent predictors of carotid plaque. (Roman et al, 2003) Similarly, Manzi et al. demonstrated that duration of lupus and disease damage (measured by SLICC-DI) were significantly associated with a higher carotid plaque index. (Manzi et al, 1999)

8.5.2 Renal disease

Renal disease is one of the most common internal organ manifestations of SLE. Both hypertension and dyslipidaemia are well described with lupus nephritis and renal disease. Lupus renal disease is also associated with increased atherosclerosis. In fact, nearly 50% of deaths in lupus patients with renal disease are attributed to CV or cerebrovascular disease. (Appel et al, 1994)

8.5.3 Autoantibody production

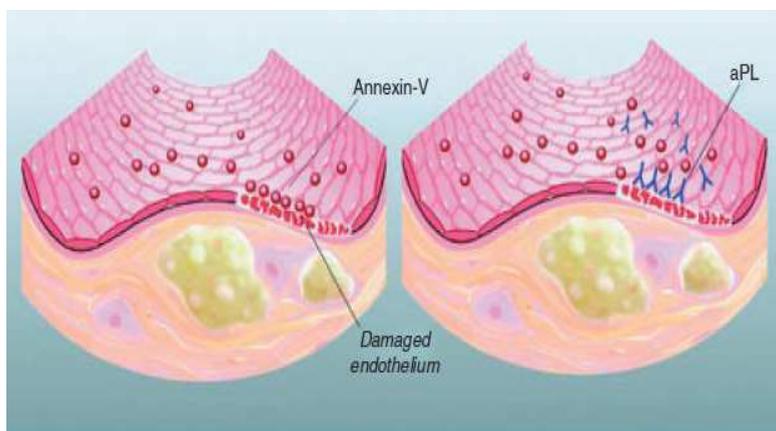
Systemic lupus erythematosus is characterized by autoantibody production. The immune reactions involving antibody production modulate atherosclerosis. Antiphospholipid antibodies and anti-oxLDL have been associated with CAD mortality in the general population. However, the relationship is nonlinear, making antibody status difficult to use as a predictor of individual risk. (Erkkila et al, 2005) Patients with SLE and secondary antiphospholipid antibody syndrome (APS) had a higher prevalence of carotid plaque than patients with primary APS. (Jimenez et al, 2005) In patients with SLE, the prevalence of anticardiolipin antibodies is quoted between 24 and 39% and for lupus anticoagulant it is quoted as 15–30%. However, only 50% of patients with the antiphospholipid antibodies will have a clinical event (defined as arterial or venous thrombosis or pregnancy morbidity), and thus have APS. (Giles & Rahman, 2009) A retrospective analysis carried out by Bessant et al. demonstrated that patients with SLE just prior to a CVD event (MI, angina, cerebrovascular accident [CVA] or peripheral vascular disease) were more likely to have the presence of lupus anticoagulant compared with patients with SLE without CVD, after controlling for

disease duration. (Bassant et al, 2006) Anti- β -2-glycoprotein I antibody has also been associated with increased risk of acute coronary syndrome in the general population. (Veres et al, 2004). Anti β -2-glycoprotein I antibodies was identified as a significant risk factor for arteriosclerosis obliterans in SLE patients, and was associated strongly with ischemic heart disease in patients with SLE. (Cederholm et al, 2005)

Annexin V plays a role in atherosclerotic lesions since it is believed to form a protective shield over thrombogenic cell surface proteins. (Fig.10) Decreased annexin V binding to the endothelium, caused by anticardiolipin IgG, was found in the sera of patients with SLE and CVD. (Cederholm et al, 2005)

In addition, antibodies against oxLDL have been found in patients with angiographic CAD. The oxidation of LDL may lead to the formation of neopeptides that bind to scavenger receptors of macrophages and lead to uptake of oxLDL, accelerating foam cell formation in the atherosclerotic plaque. The level of oxLDL was associated with arterial disease (defined as clinically evident MI, angina, peripheral claudication or thrombosis). (Frostedgard et al, 2005)

In patients with an established history of hypertension, high levels of IgM antiphosphorylcholine (anti-PC) antibodies were shown to be atheroprotective; they resulted in less progression of IMT on carotid ultrasound (OR: 0.46; 95% CI: 0.25–0.85; $p = 0.01$). (Su j et al, 2006) Decreased levels of anti-PC antibodies were observed in both SLE cases with CVD and SLE controls without CVD compared with population controls. (Skamra & Ramsey-Golman, 2010)



aPL interfere with binding to endothelium of antithrombotic Annexin V. Frostedgard JJ, *Int Med*, 2005;257(6):485-495. Copyright permission from John Wiley & Sons.

Fig. 6. Potential mechanism of atherothrombosis in systemic lupus erythematosus (SLE).

8.5.4 SLE therapy

Corticosteroids:

Corticosteroid therapy in SLE patients is often a double-edged sword. While it is still one of the most effective therapies for managing lupus disease activity, it has numerous metabolic side effects on blood pressure, blood glucose, lipids and weight. Petri et al. reported that a

change of 10 mg of prednisone leads to an increase of 7.5mg/dl of TC, a 1.1-mmHg increase in mean arterial blood pressure and a 2.5-kg weight gain. (Petri et al, 1994) Additionally, longer duration of corticosteroid therapy is associated with sub-clinical CVD (Manzi et al, 1999) and independently predicts CV events in lupus patients. (Elliott et al, 2008) Lupus patients on corticosteroids are also likely to have greater inflammatory disease burden, placing them at higher CVD risk. MacGregor et al. found a corticosteroid dose-related effect. Above a daily dose of 10 mg of prednisolone, the triglyceride (TG) and Apo B levels were elevated compared with controls without SLE, but below a daily dose of 10 mg prednisolone there was no difference between controls and SLE patients. (Macgregor et al, 1992) Similarly, Petri et al. found that prednisone of over 10 mg daily was associated with hypercholesterolemia, defined as total cholesterol of more than 200 mg/dl. (Petri, 2000) Additionally, Montreal Lupus Clinic researchers reported that SLE patients on 30 mg of corticosteroids have a 60% greater 2-year CV risk than do SLE patients with the same disease activity and traditional risk factors but not on corticosteroids. This finding emphasizes the need for corticosteroid monitoring and the use of steroid-sparing agents in the clinical care of SLE patients. (Thompson et al,2008) Patients with SLE and CVD were more likely than SLE age-matched controls (without CVD) to have taken a mean dosage of prednisone of over 7.5 mg/day ($p = 0.04$) and more likely to have been treated with pulse methylprednisolone ($p = 0.03$) (Bessant et al, 2006) A longer duration of corticosteroid use (11 vs 7 years; $p = 0.002$) was more common in the patients who had an event than in those without an event. (Manzi et al, 1997) Women with SLE who had a longer duration of prednisone use and higher cumulative dose of prednisone are more likely to have carotid plaque on ultrasound (Manzi et al,1999) and the IMT progression is associated with years of steroid use.(Thompson et al,2008)

Anti-malarial medication:

Hydroxychloroquine (HCQ) therapy has been shown to have several beneficial CV effects in SLE patients. HCQ use in SLE patients has been shown to reduce TC, LDL and TG levels. (Wallace et al, 1990)The lipid lowering effect of HCQ is greatest in younger patients (age 16–39 years) and may offset the dyslipidaemia associated with corticosteroid therapy. (Rahman et al, 1999) Lupus patients taking HCQ have had significantly lower mean glucose levels and markers of insulin resistance. (Petri, 1996) HCQ has been postulated to prevent future thrombotic events, (Erkan et al, 2002) and lupus patients on HCQ therapy are less likely than those not on it to have carotid plaque. Its protective effect on the vasculature may be in part due to inhibition of aPL-mediated platelet activation. (Roman et al, 2003)

Immunosuppressant medications:

Roman's study demonstrated that patients with carotid plaque by B-mode ultrasound were less likely to have been treated with prednisone and cyclophosphamide when analyzed by multivariate analysis. (Roman et al, 2003) Mycophenolate mofetil (MMF) has been studied in patients with renal and cardiac transplants and found to reduce allograft vasculopathy and intimal thickening compared with those treated with azathioprine, as reviewed by Gibson and Hayden.(Gibson & Hayden, 2007). While there are no specific studies regarding cardiovascular outcomes in patients with SLE who take MMF, extrapolating the transplant data suggests this may be a useful choice for treating LN. Immunosuppressant medications should be used judiciously and corticosteroid dosage

should be minimized, but control of SLE should not be sacrificed to avoid CVD risk. (Skamra & Ramsay-Goldman, 2010)

Estrogens & hormone replacement therapy

Patients with antiphospholipid antibodies are at increased risk of thrombosis. Thus, general recommendations include discontinuing estrogen usage, despite a lack of randomized, controlled trials. (Sammaritano, 2007) A prospective study evaluating patients with SLE who took hormone replacement therapy (HRT) revealed that HRT was not a risk factor for CAD, despite the presence of antiphospholipid antibodies in 74.6% of HRT users. (Hochman et al, 2009) However, the role of hormones in patients with SLE who lack antiphospholipid antibodies has been more clearly defined. Both the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) study and the LUMINA study found that exogenous hormones were safe to use in their patient populations as long as SLE was stable, and did not increase the risk of arterial thrombosis in lower risk patients. (Fernandez et al, 2007) Based on risk and needs, oral contraceptive and HRT use are recommended in properly selected patients who do not have antiphospholipid antibodies. (Skamra & Ramsay-Goldman, 2010)

8.5.5 Endothelial dysfunction

Many soluble markers of endothelial dysfunction have been studied in atherosclerosis, including cytokines, chemokines, soluble adhesion molecules and acute phase reactants. Their clinical use is limited by their instability, inadequate laboratory performance and lack of standardization at this time; however, they may prove to be a valuable tool in the future. Biochemical markers of endothelial cell activation, such as soluble thrombomodulin, von Willebrand factor and tissue plasminogen activator, are increased in patients with SLE. (Constans et al, 2003) While soluble vascular cellular adhesion molecule (sVCAM)-1 was elevated only in the patients with SLE and CVD. This is of further interest, since sVCAM-1 is associated with systemic TNF- α . There is positive correlation between TNF- α and plasma TGs, VLDL TGs and VLDL-C]. SLE patients with a higher IMT value using B-mode ultrasound had significantly higher mean plasma VEGF levels compared with controls after adjusting for age, smoking and other Framingham risk factors. (Svenungsson et al, 2003) Thus, these soluble biomarkers may have a future role in identifying SLE patients at risk for CVD. The Tie-2 receptor (a vascular-specific tyrosine kinase receptor), through its interaction with angiopoietin (Ang)-1, maintains vessel integrity, inhibits vascular leakage, suppresses inflammatory gene expression, and prevents recruitment and transmigration of leukocytes. Ang-2 has emerged as a key mediator of endothelial cell activation and facilitates endothelial cell inflammation by counterbalancing the effects of Ang-1 and disrupting these functions. (Skamra & Ramsay-Goldman, 2010) Ang-2 concentrations were elevated in hypertensive patients compared with healthy controls (4.23 ± 3.1 vs 0.88 ± 0.43 ng/ml; $p < 0.0001$); and it was particularly elevated in those patients with atherosclerosis ($p = 0.02$). Furthermore, Ang-2 concentrations correlated with other vascular markers of endothelial cell activation, including VCAM-1 and ICAM-1. Mean serum Ang-2 concentrations were markedly elevated in patients with active SLE compared with inactive SLE (8.6 vs 1.4 ng/ml; $p = 0.010$) and healthy controls (8.6 vs 1.1 ng/ml; $p < 0.001$), and Ang-2 remained significantly elevated in patients with inactive SLE compared with healthy controls. (Skamra & Ramsay-Goldman, 2010) Maintaining vascular integrity after damage is a role played by

endothelial progenitor cells (EPCs) and myelomonocytic circulating angiogenic cells. Decreased levels or abnormal function of those cells is an established atherosclerotic risk factor. (Hill et al, 2003) SLE patients possess significantly fewer numbers of circulating EPCs as well as impaired differentiation of EPCs and circulating angiogenic cells into mature endothelial cells that are capable of producing VEGF. These abnormalities are triggered by IFN- α , which induces EPC and circulating angiogenic cell apoptosis. SLE EPCs/circulating angiogenic cells have increased IFN- α expression, which might promote accelerated atherosclerosis. (Hill et al, 2003)

8.5.6 Cytokines

In addition to the relationship between TNF- α and IFN- α , other cytokines and their associated polymorphisms (IL-10 and IL-6) have also been implicated in the relationship between CVD and SLE. IL-10 has an atheroprotective role compared with TNF- α , which is atherogenic. Both IL-10 and TNF- α are seen increased in SLE patients with CVD compared with SLE patients without CVD or controls. IL-6 overproduction has been associated with SLE, CVD and C-reactive protein (CRP) elevations. Measurement of individual cytokines is laborious and may be difficult to interpret without an overall cytokine profile. The role of IL-10 and IL-6 and many other cytokines in SLE and CVD remains to be fully elucidated. (Skamra & Ramsay-Goldman, 2010)

8.5.7 CRP

In addition to its relationship with arterial stiffness, an elevated level of serum CRP has been associated with MI and stroke in the general population. Its role in risk stratification remains unclear because it might improve risk prediction beyond the traditional Framingham calculation; however, further study will be required before it can be accepted as a standard CVD risk factor. (Lloyd-Jones et al, 2006) In patients with SLE, an elevated serum CRP has been associated with the presence of carotid plaque. Elevated CRP has also been associated with the highest quartile of IMT on carotid ultrasound in SLE patients. (Manzi et al, 1999) CRP is also found to have association with cardiovascular events and SLE disease activity as measured by the Systemic Lupus Activity Measure, but not with overall damage accrual as measured by the SLICC-DI. (Szalai et al, 2005; Bertoli et al, 2008)

8.5.8 Homocysteine

Homocysteine is believed to be a toxin that results in endothelial injury and dysfunction in patients with CVD, but its exact role remains to be defined. Homocysteine may have a role in differentiating between patients with SLE and CVD and those with CVD without SLE. Patients with SLE from the Toronto Lupus Cohort had higher mean homocysteine levels compared with age-matched controls, despite having higher folate levels. Studies found that a homocysteine level above 14.1 mmol/l was an independent risk factor for development of CAD in patients with SLE after controlling for established risk factors (Svenungsson et al, 2001, Petri, 2009) Homocysteine concentration was found to be significantly higher among patients with progressive plaque compared with patients without carotid plaque. (Roman et al, 2007) In addition to SLE, renal failure is a known cause of hyperhomocysteinemia. While the role of homocysteine is not completely defined, Von Feldt suggests that it may be a useful initial test in the evaluation of SLE patients in order to determine the presence and extent of subclinical atherosclerotic disease. (Von Feldt et al, 2008)

8.6 Assessment and management

8.6.1 Assessment and management of traditional risk factors (table 1.)

Obesity

Assessment

The National Heart, Lung, and Blood Institute (NHLBI), (National Institute of Health, 1998) American Heart Association (AHA) (Smith et al, 2006) and the American College of Cardiology (ACC) recommends checking weight and height to calculate BMI, as well as waist circumference, at each visit. Waist circumference is a marker of visceral or intra-abdominal fat and should be assessed at the iliac crest. Goal BMI is recommended from 18.5 to 24.6 kg/m² and waist circumference should be <40 inches in men and <36 inches in women. (Smith et al, 2006)

Management

Preventing obesity is the first line of defense. Physicians should educate patients to avoid weight gain by promoting healthy eating and physical activity. Specific to lupus itself, aggressive control of joint and fatigue symptoms and global lupus disease activity could help facilitate physical exercise. As corticosteroid use can lead to weight gain and other metabolic risks, minimizing the corticosteroid dose by adding a steroid-sparing agent, such as HCQ, or an immunosuppressive agent may be needed. For those patients with a BMI >25 kg/m² or whose waist circumference is >40 inches in men or >35 inches in women, a combined dietary and physical exercise programs is indicated. These dietary and exercise recommendations can also be applied to patients with dyslipidaemia, hypertension and diabetes (see below).

Diet: AHA Diet and Lifestyle recommendations (Lichtenstein et al, 2006) advocate the following: a diet rich in fruits, vegetables and whole-grain, high-fiber foods, consuming fish (specifically oily fish) twice a week, limiting saturated fat to <7% (trans fat to <1%) and cholesterol to <300 mg /day by choosing lean meats and fat-free or low-fat dairy products, minimizing beverages and foods with added sugars, low or no salt diet and consuming alcohol in moderation.

Consultation with a nutritionist or dietitian is strongly encouraged. An individualized dietary plan, taking into account specific health concerns and medications, will be a powerful tool for lupus patients and their CV health. (Elliott & Manzi, 2009)

Exercise. Physicians should take every office visit as an opportunity to encourage patients to exercise. The AHA recommends 30 min of moderate-intensity (brisk walking) aerobic activity 5 days per week or 20 min of vigorous-intensity (jogging) 3 days a week for healthy adults. Haskell et al, 2007) Resistance training (weight lifting) to improve muscle strength and endurance is advocated twice per week and should include all 10 major muscle groups. Patients should be encouraged to increase their daily lifestyle activities, such as walking to the store and using stairs instead of elevators. For those with cardiac history or recent vascular surgery, physicians should provide a medically supervised exercise program. (Smith et al, 2006)

In addition to CV benefits, physical exercise may improve conditions related specifically to SLE disease. SLE patients can improve their aerobic capacity and exercise tolerance and fatigue after following an exercise program, without aggravating their SLE disease. (Clarke-Jenssen et al, 2005) Aerobic exercise can also improve quality of life in patients with SLE by improving both depression levels and global sense of well-being. (Avan & Martin, 2007)

Risk factors	Monitoring strategies	Management strategies
Obesity	Check weight, height, and waist circumference at each visit Goal BMI <25 kg/m ² Goal waist circumference <35 inches for women or <40 inches for men	Regular exercise Dietary counseling Referral to nutritionist and exercise therapist Referral to hospital- or community-based weight loss programs Lowest possible dose of corticosteroids
Dyslipidemia	Check fasting lipid panel at initial visit, then yearly If dyslipidemic, check lipids every 6 months or 6 weeks after medication changes Goal LDL <100 mg/dl Goal LDL <70 mg/dl for those with known CVD or PVD or diabetes	Encourage lifestyle modification with diet, exercise, and weight loss counseling Lowest possible dose of corticosteroids Consider hydroxychloroquine therapy Consider lipid lowering therapy for those not at LDL goal Consider ASA therapy Consider preventive cardiology evaluation
Hypertension	Check blood pressure at each visit and between visits for those on corticosteroids or NSAIDs Goal BP <130/80 mmHg	Aggressive blood pressure control Encourage lifestyle modification with diet, exercise, and weight loss counseling Addition of ACE inhibitor for those with diabetes or renal disease Lowest possible dose of corticosteroids Consider ASA therapy
Diabetes Mellitus/Insulin Resistance	Check fasting glucose yearly Consider checking fasting insulin and calculate insulin resistance Oral glucose tolerance test if needed. Goal fasting glucose <126 mg/dl Goal HbA1c <7%	Endocrinology evaluation Early aggressive therapy to maintain HbA1c <7% Encourage lifestyle modification with diet, exercise, and weight loss counseling Consider hydroxychloroquine therapy Consider ASA therapy Aggressive management of blood pressure, lipids, and other CV risk factors
Tobacco Use	Ask patient about tobacco use at each visit Goal of complete tobacco cessation	Discuss importance of tobacco cessation Assess willingness to quit Referral to tobacco cessation program Suggest pharmacotherapy Consider ASA therapy

BMI: body mass index. LDL: low-density lipoprotein. HDL: high-density lipoprotein. CVD: cardiovascular disease. PVD: peripheral vascular disease. BP: blood pressure. NSAIDs: nonsteroidal anti-inflammatory drugs. HbA1c: glycosylated hemoglobin. ASA: aspirin.

Table 1. Assessment and Management strategies of traditional risk factors in patients with SLE. (Elliot JR, Mansi S, 2009. Copyright permission from Elsevier)

Given these data, physicians should consider referring patients to an exercise physiologist or specialists in physical exercise. An individualized exercise plan that takes into account patients specific needs and limitations may help to assure their long-term commitment to being physically fit. (Elliott &Manzi, 2009)

Dyslipidaemia:

Assessment At baseline and yearly, a fasting lipid panel (TC, LDL, HDL and TG levels) should be performed on patients with SLE. It is proposed that lupus patients be considered CHD risk equivalents, similar to patients with diabetes. Accordingly, based on the National Cholesterol Education Program Adult Treatment Panel (ATP III), (National Cholesterol Education Program [NCEP], 2001) the goal cholesterol levels in lupus patients should be: TC <200 mg/dl, LDL <100 mg/dl, TG <150 mg/dl and HDL >40 mg/dl.

Management

Lifestyle modifications should be considered as first-line approach, with an emphasis on reducing saturated and transunsaturated fat and cholesterol intake and weight loss. The American Diabetes Association (ADA) and the ACC issued a consensus statement recommending both lifestyle modifications and lipid pharmacological therapy, regardless of LDL level, for all patients with known CVD or for high-risk groups, such as patients with diabetes .(Brunzell et al, 2008) They further recommended a tighter LDL goal of <70 mg/dl. There is a scarcity of lipid-lowering therapy clinical trials in SLE. Petri et al. reported an improvement in carotid IMT in SLE patients treated with atorvastatin.(Petri et al, 2006) Most do not advocate the wide-spread use of statins in all SLE patients, (Tolozza et al, 2007 but reserve its use for those with established vascular disease or diabetes.

Based on the available literature, Elliott & Manzi propose the following management of dyslipidaemia in SLE patients:

- Regardless of LDL level, corticosteroid therapy should be minimized, HCQ be considered and lifestyle modifications be initiated.
- LDL goal of <100 mg/dl or <70 mg/dl for those with sub-clinical CVD, known CV or peripheral vascular disease (PVD), or diabetes
- Consideration of lipid-lowering therapy for LDL >100 mg/dl or >70 mg/dl for those with subclinical CVD, known CVD or PVD, or diabetes

Hypertension

Assessment

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) continues to define hypertension as exceeding 140/90 mmHg. (Chobanian et al, 2003) However, the report recommends for the first time, a more stringent goal of <130/80 mmHg for patients with high-risk conditions, such as diabetes or chronic kidney disease. Based on this literature, Elliott & Manzi recommended a goal blood pressure of <130/80 mmHg for patients with SLE. Additionally, a blood pressure reading should be obtained at each physician visit and between visits for lupus patients on corticosteroids and non-steroidal anti-inflammatory drugs.

Management

Lifestyle modifications regarding diet, specifically salt restriction, exercise, weight control and alcohol moderation, is recommended for all patients with a blood pressure >140/90 mmHg. Except for those with known ischaemic heart disease or diabetes, lowering of blood

pressure is more important than the choice of anti-hypertensive agent. Anti-hypertensive therapy should also be initiated when blood pressure readings are $>140/90$ mmHg. Aggressive combination therapy is often needed to obtain blood pressure goals, and the JNC 7 recommends starting combination therapy when SBP >150 mmHg or DBP >90 mmHg. (Chobanian et al, 2003) Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers or thiazide diuretics are typically first-line therapy for hypertension. However, a beta-blocker should be used in patients with known CAD and an ACE or ARB is recommended in those with diabetes or renal disease. Corticosteroid therapy should also continue to be minimized given its relationship with blood pressure elevation. (Elliott & Manzi, 2009)

Diabetes mellitus

Assessment

All lupus patients should have a fasting glucose checked yearly. The American Diabetic Association (ADA) defines diabetes with either a fasting plasma glucose of >126 mg/dl or a glucose tolerance test of >200 mg dl. (Nathan et al, 2006) Goals of therapy should be near-normal glucose levels and a haemoglobin A1C level of $<7\%$.

Management

Lupus patients with diabetes should undergo structured diabetic education programs that emphasize aggressive lifestyle changes in diet, exercise and weight management. The ADA also recommends metformin therapy in addition to lifestyle changes for all patients newly diagnosed with diabetes. (Nathan et al, 2006) If this regimen is not effective in reaching glucose or haemoglobin A1C goals, then another oral diabetic agent or insulin should be started. Endocrinology referral should be strongly encouraged for these patients.

Other risk factors: Other CV risk factors must also be evaluated and aggressively treated. As described above, blood pressure therapy is recommended at $>140/90$ mmHg and statin therapy at LDL >100 mg /dl. All patients should be counseled on tobacco cessation and considered for aspirin therapy. HCQ should also be considered for all lupus patients with impaired glucose function and diabetes. Similarly, corticosteroid therapy should be minimized to avoid exacerbations of hyperglycaemia.

8.6.2 SLE-specific and inflammatory risk factor assessment and management

A summary of the assessment and management strategies for lupus-specific and inflammatory CV risk factors is outlined in Table 2.

8.7 Conclusion

Cardiovascular involvement in SLE may easily be overlooked until a full blown cardiac dysfunction or complication occurs.

- Cardiac involvement in SLE involves all the three layers of the heart (pericardium, myocardium, endocardium)
- Pericarditis is a common cardiac manifestation of SLE and can present rarely with cardiac tamponade being the initial presentation. Diagnosis is based on ECG and echocardiography findings. Pericarditis responds well to steroid therapy, and rarely may progress to cardiac tamponade necessitating pericardiocentesis. Refractory cases may require pericardial window.

Risk factors	Monitoring strategies	Management strategies
SLE Disease activity	Assess disease activity and medications at each visit	Lowest possible dose of corticosteroids Add steroid sparing agent if unable to lower corticosteroid dose Consider hydroxychloroquine therapy Consider ASA therap
SLE Renal disease	Assess renal parameters at each visit: BP, serum albumin, creatinine, and urinalysis Goal BP <130/80 mmHg Goal to normalize creatinine and albumin Goal proteinuria <300 mg/dl	Aggressive blood pressure control Addition of ACE inhibitor Consider ASA therapy
Antiphospholipids or Lupus Anticoagulant positivity	Check antiphospholipids, Lupus Anticoagulant, and beta 2 glycoprotein antibody status initially and as needed	Consider hydroxychloroquine therapy Consider ASA therapy
Inflammatory CV risk factors In SLE		
C-reactive protein	Consider checking as an additive predictive factor	Unclear at this time
Homocysteine	Check initially and as needed	Unclear at this time, but consider folic acid supplementation for hyperhomocysteinemia

Table 2. Summary of SLE-specific CV risk factors in patients with SLE (Elliot JR, Mansi S, 2009. Copyright permission from Elsevier)

- Myocarditis presents in 3-15% of the SLE patients clinically, but a common finding in autopsy studies. It may present with florid heart failure or subacutely as tachycardia and dyspnea. Myocarditis should be considered in patient with tachycardia and fever, with a 3rd heart sound with abnormal ECG in those with a new murmurs or conduction disturbances and those with congestive heart failure. Treatment is with high dose steroid and with IV cyclophosphamide in refractory cases in addition to antifailure therapy. Anticoagulation should be considered in those with cardiomyopathy.
- Valvular heart disease due to Libman Sacks endocarditis is found less frequently in the era of corticosteroids. The mitral valve is the most common valve involved followed by the the aortic valve. Echocardiography is the modality of choice for diagnosis. Use of steroids to shinken the vegetation is controversial and as may led to fibrosis. Bacterial prophylaxis is indicated in patients with significant regurgitation with jet lesions even in the absence of nodules.

- Arrhythmia and conduction defects occur in 10% of the patients with SLE either as a consequence of pericarditis or myocarditis or involvement of the conduction system by fibrosis or atherosclerosis. AntiSSA/RO associated cardiac manifestations include transient fetal heart block, QTc prolongation, sinus bradycardis, late on-set cardiomyopathy, endocardial fibroelastosis and cardiac malformations. In the adult heart may cause QTc prolongation in lupus patients.
- Coronary arteritis presents with angina or myocardial infarction in a child or a young adult who do not have a long history of corticosteroid therapy. Serial coronary angiography is the proposed diagnostic modality. Corticosteroids may have rapid relief of the angina and may need cyclophosphamide.
- Premature atherosclerosis, cardiovascular risk factors and cardiovascular events all occur at a younger age in patients with SLE compared with the general population.
- After controlling for traditional Framingham risk factors, patients with SLE still have a 7.5-fold (95% CI: 5.1-10.4) excess risk of overall coronary heart disease. This suggests that SLE itself carries an independent risk for CVD and exposes the failure of the Framingham risk calculator to capture a younger at-risk population.
- Traditional risk factors, lupus related, and novel inflammatory CV risk factors are implicated in the pathogenesis of premature atherosclerosis.
- Treatment recommendations for patients with SLE are based on other high-risk populations since there are no randomized, controlled trials that demonstrate the efficacy of interventions on cardiovascular events in SLE.
- Lifestyle modifications and/or statins should be used to lower LDL-cholesterol below 100 mg/dl as suggested in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines.
- Hypertension should be treated to maintain a blood pressure less than 130/80 mmHg. First-choice medication for patients with SLE should probably be angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), especially in patients with concomitant lupus nephritis or diabetes mellitus.
- Low-dose daily aspirin therapy is recommended in patients with SLE barring an absolute contraindication.
- Use of antimalarial medications in all patients with SLE is recommended.
- Use of corticosteroids should be minimized and immunosuppressant medications should be used judiciously, but control of SLE should not be sacrificed to minimize CVD risk.
- Smoking cessation, regular aerobic exercise and maintaining a normal BMI are recommended in all patients with SLE.

9. Acknowledgments

The work to produce this chapter was supported by Alzaidi's Chair of research in rheumatic diseases- Umm Alqura University.

10. References

- Alves, J. D., & Grima, B. (2003). Oxidative stress in systemic lupus erythematosus and antiphospholipid syndrome: a gateway to atherosclerosis. *Curr Rheumatol Rep*, 5(5), 383-390.

- Appel, G. B., Pirani, C. L., & D'Agati, V. (1994). Renal vascular complications of systemic lupus erythematosus. *J Am Soc Nephrol*, 4(8), 1499-1515.
- Appenzeller, S., Pineau, C., & Clarke, A. (2011). Acute lupus myocarditis: Clinical features and outcome. *Lupus*, 20(9), 981-988.
- Asanuma, Y., Oeser, A., Shintani, A. K., Turner, E., Olsen, N., Fazio, S., Linton, M. F., Raggi, P., & Stein, C. M. (2003). Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med*, 349(25), 2407-2415.
- Ashrafi, R., Garg, P., McKay, E., Gosney, J., Chuah, S., & Davis, G. (2011). Aggressive cardiac involvement in systemic lupus erythematosus: a case report and a comprehensive literature review. *Cardiol Res Pract*, 2011, 578390.
- Ayan, C., & Martin, V. (2007). Systemic lupus erythematosus and exercise. *Lupus*, 16(1), 5-9.
- Batucu, J. R., Ames, P. R., Isenberg, D. A., & Alves, J. D. (2007). Antibodies toward high-density lipoprotein components inhibit paraoxonase activity in patients with systemic lupus erythematosus. *Ann N Y Acad Sci*, 1108, 137-146.
- Bautista, L. E., Vera, L. M., Arenas, I. A., & Gamarra, G. (2005). Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. *J Hum Hypertens*, 19(2), 149-154.
- Becker-Merok, A., & Nossent, J. (2009). Prevalence, predictors and outcome of vascular damage in systemic lupus erythematosus. *Lupus*, 18(6), 508-515.
- Berg, G., Bodet, J., Webb, K., Williams, G., Palmer, D., Ruoff, B., & Pearson, A. (1985). Systemic lupus erythematosus presenting as isolated congestive heart failure. *J Rheumatol*, 12(6), 1182-1185.
- Bernatsky, S., Boivin, J. F., Joseph, L., Manzi, S., Ginzler, E., Gladman, D. D., Urowitz, M., Fortin, P. R., Petri, M., Barr, S., Gordon, C., Bae, S. C., Isenberg, D., Zoma, A., Aranow, C., Dooley, M. A., Nived, O., Sturfelt, G., Steinsson, K., Alarcon, G., Senecal, J. L., Zummer, M., Hanly, J., Ensworth, S., Pope, J., Edworthy, S., Rahman, A., Sibley, J., El-Gabalawy, H., McCarthy, T., St Pierre, Y., Clarke, A., & Ramsey-Goldman, R. (2006). Mortality in systemic lupus erythematosus. *Arthritis Rheum*, 54(8), 2550-2557.
- Bertoli, A. M., Vila, L. M., Reveille, J. D., & Alarcon, G. S. (2008). Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): LXI. Value of C-reactive protein as a marker of disease activity and damage. *J Rheumatol*, 35(12), 2355-2358.
- Bessant, R., Duncan, R., Ambler, G., Swanton, J., Isenberg, D. A., Gordon, C., & Rahman, A. (2006). Prevalence of conventional and lupus-specific risk factors for cardiovascular disease in patients with systemic lupus erythematosus: A case-control study. *Arthritis Rheum*, 55(6), 892-899.
- Bharati, S., de la Fuente, D. J., Kallen, R. J., Freij, Y., & Lev, M. (1975). Conduction system in systemic lupus erythematosus with atrioventricular block. *Am J Cardiol*, 35(2), 299-304.
- Bidani, A. K., Roberts, J. L., Schwartz, M. M., & Lewis, E. J. (1980). Immunopathology of cardiac lesions in fatal systemic lupus erythematosus. *Am J Med*, 69(6), 849-858.

- Borba, E. F., Santos, R. D., Bonfa, E., Vinagre, C. G., Pileggi, F. J., Cossermelli, W., & Maranhao, R. C. (1994). Lipoprotein(a) levels in systemic lupus erythematosus. *J Rheumatol*, 21(2), 220-223.
- Borba, E. F., & Bonfa, E. (1997). Dyslipoproteinemias in systemic lupus erythematosus: influence of disease, activity, and anticardiolipin antibodies. *Lupus*, 6(6), 533-539.
- Borenstein, D. G., Fye, W. B., Arnett, F. C., & Stevens, M. B. (1978). The myocarditis of systemic lupus erythematosus: association with myositis. *Ann Intern Med*, 89(5 Pt 1), 619-624.
- Brigden, W., Bywaters, E. G., Lessof, M. H., & Ross, I. P. (1960). The heart in systemic lupus erythematosus. *Br Heart J*, 22, 1-16.
- Bruce, I. N., Urowitz, M. B., Gladman, D. D., Ibanez, D., & Steiner, G. (2003). Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. *Arthritis Rheum*, 48(11), 3159-3167.
- Brunzell, J. D., Davidson, M., Furberg, C. D., Goldberg, R. B., Howard, B. V., Stein, J. H., & Witztum, J. L. (2008). Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*, 51(15), 1512-1524.
- Bulkley, B. H., & Roberts, W. C. (1975). The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy. A study of 36 necropsy patients. *Am J Med*, 58(2), 243-264.
- Busteed, S., Sparrow, P., Molloy, C., & Molloy, M. G. (2004). Myocarditis as a prognostic indicator in systemic lupus erythematosus. *Postgrad Med J*, 80(944), 366-367.
- Calabresi, L., Franceschini, G., Sirtori, C. R., De Palma, A., Saresella, M., Ferrante, P., & Taramelli, D. (1997). Inhibition of VCAM-1 expression in endothelial cells by reconstituted high density lipoproteins. *Biochem Biophys Res Commun*, 238(1), 61-65.
- Cardoso, C. R., Sales, M. A., Papi, J. A., & Salles, G. F. (2005). QT-interval parameters are increased in systemic lupus erythematosus patients. *Lupus*, 14(10), 846-852.
- Cederholm, A., Svenungsson, E., Jensen-Urstad, K., Trollmo, C., Ulfgren, A. K., Swedenborg, J., Fei, G. Z., & Frostegard, J. (2005). Decreased binding of annexin v to endothelial cells: a potential mechanism in atherothrombosis of patients with systemic lupus erythematosus. *Arterioscler Thromb Vasc Biol*, 25(1), 198-203.
- Cervera, R., Khamashta, M. A., Font, J., Reyes, P. A., Vianna, J. L., Lopez-Soto, A., Amigo, M. C., Asherson, R. A., Azqueta, M., Pare, C., & et al. (1991). High prevalence of significant heart valve lesions in patients with the 'primary' antiphospholipid syndrome. *Lupus*, 1(1), 43-47.
- Cervera, R., Font, J., Pare, C., Azqueta, M., Perez-Villa, F., Lopez-Soto, A., & Ingelmo, M. (1992). Cardiac disease in systemic lupus erythematosus: prospective study of 70 patients. *Ann Rheum Dis*, 51(2), 156-159.
- Chen, C. Y., Wang, F. L., & Lin, C. C. (2006). Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. *Clin Toxicol (Phila)*, 44(2), 173-175.
- Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., Jones, D. W., Materson, B. J., Oparil, S., Wright, J. T., Jr., & Roccella, E. J. (2003). The

- Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*, 289(19), 2560-2572.
- Chung, L., Berry, G. J., & Chakravarty, E. F. (2005). Giant cell myocarditis: a rare cardiovascular manifestation in a patient with systemic lupus erythematosus. *Lupus*, 14(2), 166-169.
- Clarke-Jenssen, A. C., Fredriksen, P. M., Lilleby, V., & Mengshoel, A. M. (2005). Effects of supervised aerobic exercise in patients with systemic lupus erythematosus: a pilot study. *Arthritis Rheum*, 53(2), 308-312.
- Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. In. (1998), vol. 6 (pp. 51S-209S): National Institutes of Health.
- Constans, J., Dupuy, R., Blann, A. D., Resplandy, F., Seigneur, M., Renard, M., Longy-Boursier, M., Schaefferbeke, T., Guerin, V., Boisseau, M. R., & Conri, C. (2003). Anti-endothelial cell autoantibodies and soluble markers of endothelial cell dysfunction in systemic lupus erythematosus. *J Rheumatol*, 30(9), 1963-1966.
- Cooper, L. T., Jr., Berry, G. J., & Shabetai, R. (1997). Idiopathic giant-cell myocarditis--natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. *N Engl J Med*, 336(26), 1860-1866.
- Cooper, L. T., Baughman, K. L., Feldman, A. M., Frustaci, A., Jessup, M., Kuhl, U., Levine, G. N., Narula, J., Starling, R. C., Towbin, J., & Virmani, R. (2007). The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *J Am Coll Cardiol*, 50(19), 1914-1931.
- Costedoat-Chalumeau, N., Geogin-Lavialle, S., Amoura, Z., & Piette, J. C. (2005). Anti-SSA/Ro and anti-SSB/La antibody-mediated congenital heart block. *Lupus*, 14(9), 660-664.
- Daniel, L., Sichez, H., Giorgi, R., Dussol, B., Figarella-Branger, D., Pellissier, J. F., & Berland, Y. (2001). Tubular lesions and tubular cell adhesion molecules for the prognosis of lupus nephritis. *Kidney Int*, 60(6), 2215-2221.
- Doria, A., Shoenfeld, Y., Wu, R., Gambari, P. F., Puato, M., Ghirardello, A., Gilburd, B., Corbanese, S., Patnaik, M., Zampieri, S., Peter, J. B., Favaretto, E., Iaccarino, L., Sherer, Y., Todesco, S., & Pauletto, P. (2003). Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis*, 62(11), 1071-1077.
- Edwards, M. H., Pierangeli, S., Liu, X., Barker, J. H., Anderson, G., & Harris, E. N. (1997). Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. *Circulation*, 96(12), 4380-4384.
- Eisen, A., Arnson, Y., Dovrish, Z., Hadary, R., & Amital, H. (2009). Arrhythmias and conduction defects in rheumatological diseases--a comprehensive review. *Semin Arthritis Rheum*, 39(3), 145-156.

- Elliott J.R., Manzi, S., Sattar A, et al. (2008). Carotid intima-media thickness and plaque predict future cardiovascular events in women with systemic lupus erythematosus. *Arthritis Rheum*, 58(9 Suppl), Abstract 669
- Elliott, J. R., & Manzi, S. (2009). Cardiovascular risk assessment and treatment in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol*, 23(4), 481-494.
- Erkan, D., Yazici, Y., Peterson, M. G., Sammaritano, L., & Lockshin, M. D. (2002). A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. *Rheumatology (Oxford)*, 41(8), 924-929.
- Erkkila, A. T., Narvanen, O., Lehto, S., Uusitupa, M. I., & Yla-Herttuala, S. (2005). Antibodies against oxidized LDL and cardioliipin and mortality in patients with coronary heart disease. *Atherosclerosis*, 183(1), 157-162.
- Esdaile, J. M., Abrahamowicz, M., Grodzicky, T., Li, Y., Panaritis, C., du Berger, R., Cote, R., Grover, S. A., Fortin, P. R., Clarke, A. E., & Senecal, J. L. (2001). Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum*, 44(10), 2331-2337.
- Fernandez, M., Calvo-Alen, J., Alarcon, G. S., Roseman, J. M., Bastian, H. M., Fessler, B. J., McGwin, G., Jr., Vila, L. M., Sanchez, M. L., & Reveille, J. D. (2005). Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXI. Disease activity, damage accrual, and vascular events in pre- and postmenopausal women. *Arthritis Rheum*, 52(6), 1655-1664.
- Fernandez, M., Calvo-Alen, J., Bertoli, A. M., Bastian, H. M., Fessler, B. J., McGwin, G., Jr., Reveille, J. D., Vila, L. M., & Alarcon, G. S. (2007). Systemic lupus erythematosus in a multiethnic US cohort (LUMINA L II): relationship between vascular events and the use of hormone replacement therapy in postmenopausal women. *J Clin Rheumatol*, 13(5), 261-265.
- Frostedgard, J., Svenungsson, E., Wu, R., Gunnarsson, I., Lundberg, I. E., Klareskog, L., Horkko, S., & Witztum, J. L. (2005). Lipid peroxidation is enhanced in patients with systemic lupus erythematosus and is associated with arterial and renal disease manifestations. *Arthritis Rheum*, 52(1), 192-200.
- Galve, E., Candell-Riera, J., Pigrau, C., Permanyer-Miralda, G., Garcia-Del-Castillo, H., & Soler-Soler, J. (1988). Prevalence, morphologic types, and evolution of cardiac valvular disease in systemic lupus erythematosus. *N Engl J Med*, 319(13), 817-823.
- Garcia-Gonzalez, A., Gonzalez-Lopez, L., Valera-Gonzalez, I. C., Cardona-Munoz, E. G., Salazar-Paramo, M., Gonzalez-Ortiz, M., Martinez-Abundis, E., & Gamez-Nava, J. I. (2002). Serum leptin levels in women with systemic lupus erythematosus. *Rheumatol Int*, 22(4), 138-141.
- Gardner, S. Y., McGee, J. K., Kodavanti, U. P., Ledbetter, A., Everitt, J. I., Winsett, D. W., Doerfler, D. L., & Costa, D. L. (2004). Emission-particle-induced ventilatory abnormalities in a rat model of pulmonary hypertension. *Environ Health Perspect*, 112(8), 872-878.
- Gehi, A., Webb, A., Nolte, M., & Davis, J., Jr. (2003). Treatment of systemic lupus erythematosus-associated type B insulin resistance syndrome with cyclophosphamide and mycophenolate mofetil. *Arthritis Rheum*, 48(4), 1067-1070.

- Gibson, W. T., & Hayden, M. R. (2007). Mycophenolate mofetil and atherosclerosis: results of animal and human studies. *Ann N Y Acad Sci*, 1110, 209-221.
- Giles, I., & Rahman, A. (2009). How to manage patients with systemic lupus erythematosus who are also antiphospholipid antibody positive. *Best Pract Res Clin Rheumatol*, 23(4), 525-537.
- Gladman, D. D., Hussain, F., Ibanez, D., & Urowitz, M. B. (2002). The nature and outcome of infection in systemic lupus erythematosus. *Lupus*, 11(4), 234-239.
- Gladman DD, Urowitz MB. (2002) Prognosis, mortality, and morbidity in systemic lupus erythematosus. In: *Dubois' Lupus Erythematosus*, Wallace DJ, Hahn BH, (ed), 1255-1273, Lippincott Williams & Wilkins, ISBN 978-0-7897-9394, Philadelphia, USA
- Godeau, P., Guillevin, L., Fechner, J., Herreman, G., & Wechsler, B. (1981). Cardiac involvement in systemic lupus erythematosus. 103 cases (author's transl). *Nouv Presse Med*, 10(26), 2175-2178.
- Graham, I, A. D., Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. (2007). European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Atherosclerosis*, 149(1), 1-45.
- Griffith, G. C., & Vural, I. L. (1951). Acute and subacute disseminated lupus erythematosus; a correlation of clinical and postmortem findings in eighteen cases. *Circulation*, 3(4), 492-500.
- Guzman, J., Cardiel, M. H., Arce-Salinas, A., & Alarcon-Segovia, D. (1994). The contribution of resting heart rate and routine blood tests to the clinical assessment of disease activity in systemic lupus erythematosus. *J Rheumatol*, 21(10), 1845-1848.
- Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*, 352(16), 1685-1695.
- Haskell, W. L., Lee, I. M., Pate, R. R., Powell, K. E., Blair, S. N., Franklin, B. A., Macera, C. A., Heath, G. W., Thompson, P. D., & Bauman, A. (2007). Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*, 116(9), 1081-1093.
- Heibel, R. H., O'Toole, J. D., Curtiss, E. I., Medsger, T. A., Jr., Reddy, S. P., & Shaver, J. A. (1976). Coronary arteritis in systemic lupus erythematosus. *Chest*, 69(5), 700-703.
- Hejtmancik, M. R., Wright, J. C., Quint, R., & Jennings, F. L. (1964). The Cardiovascular Manifestations of Systemic Lupus Erythematosus. *Am Heart J*, 68, 119-130.
- Herlitz, H., Edeno, C., Mulec, H., Westberg, G., & Aurell, M. (1984). Captopril treatment of hypertension and renal failure in systemic lupus erythematosus. *Nephron*, 38(4), 253-256.
- Hill, J. M., Zalos, G., Halcox, J. P., Schenke, W. H., Waclawiw, M. A., Quyyumi, A. A., & Finkel, T. (2003). Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med*, 348(7), 593-600.
- Hochman, J., Urowitz, M. B., Ibanez, D., & Gladman, D. D. (2009). Hormone replacement therapy in women with systemic lupus erythematosus and risk of cardiovascular disease. *Lupus*, 18(4), 313-317.
- Jimenez, S., Garcia-Criado, M. A., Tassies, D., Reverter, J. C., Cervera, R., Gilabert, M. R., Zambon, D., Ros, E., Bru, C., & Font, J. (2005). Preclinical vascular disease in

- systemic lupus erythematosus and primary antiphospholipid syndrome. *Rheumatology (Oxford)*, 44(6), 756-761.
- Karp, I., Abrahamowicz, M., Fortin, P. R., Pilote, L., Neville, C., Pineau, C. A., & Esdaile, J. M. (2008). Recent corticosteroid use and recent disease activity: independent determinants of coronary heart disease risk factors in systemic lupus erythematosus? *Arthritis Rheum*, 59(2), 169-175.
- Khamashta, M. A., Cervera, R., Asherson, R. A., Font, J., Gil, A., Coltart, D. J., Vazquez, J. J., Pare, C., Ingelmo, M., Oliver, J., & et al. (1990). Association of antibodies against phospholipids with heart valve disease in systemic lupus erythematosus. *Lancet*, 335(8705), 1541-1544.
- Kong, T. Q., Kellum, R. E., & Haserick, J. R. (1962). Clinical diagnosis of cardiac involvement in systemic lupus erythematosus. A correlation of clinical and autopsy findings in thirty patients. *Circulation*, 26, 7-11.
- Korbet, S. M., Schwartz, M. M., & Lewis, E. J. (1984). Immune complex deposition and coronary vasculitis in systemic lupus erythematosus. Report of two cases. *Am J Med*, 77(1), 141-146.
- Korkmaz, C., Cansu, D. U., & Kasifoglu, T. (2007). Myocardial infarction in young patients (< or =35 years of age) with systemic lupus erythematosus: a case report and clinical analysis of the literature. *Lupus*, 16(4), 289-297.
- Larsson, P. T., Hallerstam, S., Rosfors, S., & Wallen, N. H. (2005). Circulating markers of inflammation are related to carotid artery atherosclerosis. *Int Angiol*, 24(1), 43-51.
- Lalani, A.L., Hatfield G. A. (2004) Imaging Finding in Systemic Lupus Erythematosus. *RadioGraphics*, 24:1069-1086
- Leung, W. H., Wong, K. L., Lau, C. P., Wong, C. K., & Cheng, C. H. (1990). Cardiac abnormalities in systemic lupus erythematosus: a prospective M-mode, cross-sectional and Doppler echocardiographic study. *Int J Cardiol*, 27(3), 367-375.
- Leung, W. H., Wong, K. L., Lau, C. P., Wong, C. K., & Liu, H. W. (1990). Association between antiphospholipid antibodies and cardiac abnormalities in patients with systemic lupus erythematosus. *Am J Med*, 89(4), 411-419.
- Lichtenstein, A. H., Appel, L. J., Brands, M., Carnethon, M., Daniels, S., Franch, H. A., Franklin, B., Kris-Etherton, P., Harris, W. S., Howard, B., Karanja, N., Lefevre, M., Rudel, L., Sacks, F., Van Horn, L., Winston, M., & Wylie-Rosett, J. (2006). Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*, 114(1), 82-96.
- Lloyd-Jones, D. M., Liu, K., Tian, L., & Greenland, P. (2006). Narrative review: Assessment of C-reactive protein in risk prediction for cardiovascular disease. *Ann Intern Med*, 145(1), 35-42.
- MacGregor, A. J., Dhillon, V. B., Binder, A., Forte, C. A., Knight, B. C., Betteridge, D. J., & Isenberg, D. A. (1992). Fasting lipids and anticardiolipin antibodies as risk factors for vascular disease in systemic lupus erythematosus. *Ann Rheum Dis*, 51(2), 152-155.
- Mandell, B. F. (1987). Cardiovascular involvement in systemic lupus erythematosus. *Semin Arthritis Rheum*, 17(2), 126-141.

- Manzi, S., Meilahn, E. N., Rairie, J. E., Conte, C. G., Medsger, T. A., Jr., Jansen-McWilliams, L., D'Agostino, R. B., & Kuller, L. H. (1997). Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol*, 145(5), 408-415.
- Manzi, S., Selzer, F., Sutton-Tyrrell, K., Fitzgerald, S. G., Rairie, J. E., Tracy, R. P., & Kuller, L. H. (1999). Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum*, 42(1), 51-60.
- Martorell, E. A., Hong, C., Rust, D. W., Salomon, R. N., Krishnamani, R., Patel, A. R., & Kalish, R. A. (2008). A 32-year-old woman with arthralgias and severe hypotension. *Arthritis Rheum*, 59(11), 1670-1675.
- McMahon, M., Grossman, J., FitzGerald, J., Dahlin-Lee, E., Wallace, D. J., Thong, B. Y., Badsha, H., Kalunian, K., Charles, C., Navab, M., Fogelman, A. M., & Hahn, B. H. (2006). Proinflammatory high-density lipoprotein as a biomarker for atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum*, 54(8), 2541-2549.
- McMahon, M., Grossman, J., FitzGerald, N., Ragavendra, N., Charles, C., Chen, W., Watson, K., Hahn, B. (2006). The novel biomarker proinflammatory HDL is associated with carotid artery plaque in women with SLE. *Arthritis Rheum*, (Abstract).
- McMahon, M., Hahn, B. V. (2007). Atherosclerosis and systemic lupus erythematosus: mechanistic basis of association. *Current Opinion in Immunology*, 19:633-639.
- Mikdashi, J., Handwerker, B., Langenberg, P., Miller, M., & Kittner, S. (2007). Baseline disease activity, hyperlipidemia, and hypertension are predictive factors for ischemic stroke and stroke severity in systemic lupus erythematosus. *Stroke*, 38(2), 281-285.
- Miyauchi, T., & Masaki, T. (1999). Pathophysiology of endothelin in the cardiovascular system. *Annu Rev Physiol*, 61, 391-415.
- Nagore, E., Requena, C., Sevilla, A., Coll, J., Costa, D., Botella-Estrada, R., Sanmartin, O., Serra-Guillen, C., & Guillen, C. (2004). Thickness of healthy and affected skin of children with port wine stains: potential repercussions on response to pulsed dye laser treatment. *Dermatol Surg*, 30(12 Pt 1), 1457-1461.
- Nakano, M., Ueno, M., Hasegawa, H., Watanabe, T., Kuroda, T., Ito, S., & Arakawa, M. (1998). Renal haemodynamic characteristics in patients with lupus nephritis. *Ann Rheum Dis*, 57(4), 226-230.
- Nathan, D. M., Buse, J. B., Davidson, M. B., Heine, R. J., Holman, R. R., Sherwin, R., & Zinman, B. (2006). Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*, 29(8), 1963-1972.
- Navab, M., Berliner, J. A., Watson, A. D., Hama, S. Y., Territo, M. C., Lusis, A. J., Shih, D. M., Van Lenten, B. J., Frank, J. S., Demer, L. L., Edwards, P. A., & Fogelman, A. M. (1996). The Yin and Yang of oxidation in the development of the fatty streak. A review based on the 1994 George Lyman Duff Memorial Lecture. *Arterioscler Thromb Vasc Biol*, 16(7), 831-842.

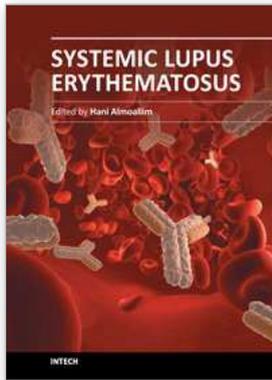
- Navab, M., Hama, S. Y., Anantharamaiah, G. M., Hassan, K., Hough, G. P., Watson, A. D., Reddy, S. T., Sevanian, A., Fonarow, G. C., & Fogelman, A. M. (2000). Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: steps 2 and 3. *J Lipid Res*, 41(9), 1495-1508.
- Nesher, G., Ilany, J., Rosenmann, D., & Abraham, A. S. (1997). Valvular dysfunction in antiphospholipid syndrome: prevalence, clinical features, and treatment. *Semin Arthritis Rheum*, 27(1), 27-35.
- Nikpour, M., Urowitz, M. B., & Gladman, D. D. (2005). Premature atherosclerosis in systemic lupus erythematosus. *Rheum Dis Clin North Am*, 31(2), 329-354, vii-viii.
- Nord, J. E., Shah, P. K., Rinaldi, R. Z., & Weisman, M. H. (2004). Hydroxychloroquine cardiotoxicity in systemic lupus erythematosus: a report of 2 cases and review of the literature. *Semin Arthritis Rheum*, 33(5), 336-351.
- Ohara, N., Miyata, T., Kurata, A., Oshiro, H., Sato, O., & Shigematsu, H. (2000). Ten years' experience of aortic aneurysm associated with systemic lupus erythematosus. *Eur J Vasc Endovasc Surg*, 19(3), 288-293.
- Okin, P. M., Devereux, R. B., Howard, B. V., Fabsitz, R. R., Lee, E. T., & Welty, T. K. (2000). Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians: The Strong Heart Study. *Circulation*, 101(1), 61-66.
- Petri, M. (1996). Hydroxychloroquine use in the Baltimore Lupus Cohort: effects on lipids, glucose and thrombosis. *Lupus*, 5 Suppl 1, S16-22.
- Petri, M. (2000). Detection of coronary artery disease and the role of traditional risk factors in the Hopkins Lupus Cohort. *Lupus*, 9(3), 170-175.
- Petri, M., Genovese, M., Engle, E., & Hochberg, M. (1991). Definition, incidence, and clinical description of flare in systemic lupus erythematosus. A prospective cohort study. *Arthritis Rheum*, 34(8), 937-944.
- Petri, M., Perez-Gutthann, S., Spence, D., & Hochberg, M. C. (1992). Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med*, 93(5), 513-519.
- Petri, M., Lakatta, C., Magder, L., & Goldman, D. (1994). Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. *Am J Med*, 96(3), 254-259.
- Petri, M. (2004). Cardiovascular Systemic Lupus Erythematosus, *Systemic Lupus Erythematosus*, Robert G. Lahita, (Ed) 913-941, Elsevier, ISBN 0-12-433901-8, USA
- Petri, M., Kim, M. Y., Kalunian, K. C., Grossman, J., Hahn, B. H., Sammaritano, L. R., Lockshin, M., Merrill, J. T., Belmont, H. M., Askanase, A. D., McCune, W. J., Heath-Holmes, M., Dooley, M. A., Von Feldt, J., Friedman, A., Tan, M., Davis, J., Cronin, M., Diamond, B., Mackay, M., Sigler, L., Fillius, M., Rupel, A., Licciardi, F., & Buyon, J. P. (2005). Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med*, 353(24), 2550-2558.
- Petri, M. A., Kiani, A. N., Post, W., Christopher-Stine, L., & Magder, L. S. (2011). Lupus Atherosclerosis Prevention Study (LAPS). *Ann Rheum Dis*, 70(5), 760-765.

- Pons-Estel, G. J., Gonzalez, L. A., Zhang, J., Burgos, P. I., Reveille, J. D., Vila, L. M., & Alarcon, G. S. (2009). Predictors of cardiovascular damage in patients with systemic lupus erythematosus: data from LUMINA (LXVIII), a multiethnic US cohort. *Rheumatology (Oxford)*, 48(7), 817-822.
- Rahman, P., Gladman, D. D., Urowitz, M. B., Yuen, K., Hallett, D., & Bruce, I. N. (1999). The cholesterol lowering effect of antimalarial drugs is enhanced in patients with lupus taking corticosteroid drugs. *J Rheumatol*, 26(2), 325-330.
- Roman, M. J., Shanker, B. A., Davis, A., Lockshin, M. D., Sammaritano, L., Simantov, R., Crow, M. K., Schwartz, J. E., Paget, S. A., Devereux, R. B., & Salmon, J. E. (2003). Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med*, 349(25), 2399-2406.
- Roman, M. J., Devereux, R. B., Schwartz, J. E., Lockshin, M. D., Paget, S. A., Davis, A., Crow, M. K., Sammaritano, L., Levine, D. M., Shankar, B. A., Moeller, E., & Salmon, J. E. (2005). Arterial stiffness in chronic inflammatory diseases. *Hypertension*, 46(1), 194-199.
- Roman, M. J., Crow, M. K., Lockshin, M. D., Devereux, R. B., Paget, S. A., Sammaritano, L., Levine, D. M., Davis, A., & Salmon, J. E. (2007). Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum*, 56(10), 3412-3419.
- Roman, M. J., & Salmon, J. E. (2007). Cardiovascular manifestations of rheumatologic diseases. *Circulation*, 116(20), 2346-2355.
- Rosenbaum, E., Krebs, E., Cohen, M., Tiliakos, A., & Derk, C. T. (2009). The spectrum of clinical manifestations, outcome and treatment of pericardial tamponade in patients with systemic lupus erythematosus: a retrospective study and literature review. *Lupus*, 18(7), 608-612.
- Ryan, M. J. (2009). The pathophysiology of hypertension in systemic lupus erythematosus. *Am J Physiol Regul Integr Comp Physiol*, 296(4), R1258-1267.
- Sammaritano, L. R. (2007). Therapy insight: guidelines for selection of contraception in women with rheumatic diseases. *Nat Clin Pract Rheumatol*, 3(5), 273-281; quiz 305-276.
- Saremi, F., Ashikyan, O., Saggarr, R., Vu, J., & Nunez, M. E. (2007). Utility of cardiac MRI for diagnosis and post-treatment follow-up of lupus myocarditis. *Int J Cardiovasc Imaging*, 23(3), 347-352.
- Selzer, F., Sutton-Tyrrell, K., Fitzgerald, S. G., Pratt, J. E., Tracy, R. P., Kuller, L. H., & Manzi, S. (2004). Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. *Arthritis Rheum*, 50(1), 151-159.
- Shapiro, R. F., Gamble, C. N., Wiesner, K. B., Castles, J. J., Wolf, A. W., Hurley, E. J., & Salel, A. F. (1977). Immunopathogenesis of Libman-Sacks endocarditis. Assessment by light and immunofluorescent microscopy in two patients. *Ann Rheum Dis*, 36(6), 508-516.
- Shearn, M. A. (1959). The heart in systemic lupus erythematosus. *Am Heart J*, 58, 452-466.

- Sherer, Y., Levy, Y., & Shoenfeld, Y. (1999). Marked improvement of severe cardiac dysfunction after one course of intravenous immunoglobulin in a patient with systemic lupus erythematosus. *Clin Rheumatol*, 18(3), 238-240.
- Skamra, C., & Ramsey-Goldman, R. (2010). Management of cardiovascular complications in systemic lupus erythematosus. *Int J Clin Rheumtol*, 5(1), 75-100.
- Smith, S. C., Jr., Allen, J., Blair, S. N., Bonow, R. O., Brass, L. M., Fonarow, G. C., Grundy, S. M., Hiratzka, L., Jones, D., Krumholz, H. M., Mosca, L., Pasternak, R. C., Pearson, T., Pfeffer, M. A., & Taubert, K. A. (2006). AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*, 113(19), 2363-2372.
- Straaton, K. V., Chatham, W. W., Reveille, J. D., Koopman, W. J., & Smith, S. H. (1988). Clinically significant valvular heart disease in systemic lupus erythematosus. *Am J Med*, 85(5), 645-650.
- Su, J., Georgiades, A., Wu, R., Thulin, T., de Faire, U., & Frostegard, J. (2006). Antibodies of IgM subclass to phosphorylcholine and oxidized LDL are protective factors for atherosclerosis in patients with hypertension. *Atherosclerosis*, 188(1), 160-166.
- Svenungsson, E., Jensen-Urstad, K., Heimburger, M., Silveira, A., Hamsten, A., de Faire, U., Witztum, J. L., & Frostegard, J. (2001). Risk factors for cardiovascular disease in systemic lupus erythematosus. *Circulation*, 104(16), 1887-1893.
- Svenungsson, E., Fei, G. Z., Jensen-Urstad, K., de Faire, U., Hamsten, A., & Frostegard, J. (2003). TNF-alpha: a link between hypertriglyceridaemia and inflammation in SLE patients with cardiovascular disease. *Lupus*, 12(6), 454-461.
- Svenungsson, E., Cederholm, A., Jensen-Urstad, K., Fei, G. Z., de Faire, U., & Frostegard, J. (2008). Endothelial function and markers of endothelial activation in relation to cardiovascular disease in systemic lupus erythematosus. *Scand J Rheumatol*, 37(5), 352-359.
- Szalai, A. J., Alarcon, G. S., Calvo-Alen, J., Toloza, S. M., McCrory, M. A., Edberg, J. C., McGwin, G., Jr., Bastian, H. M., Fessler, B. J., Vila, L. M., Kimberly, R. P., & Reveille, J. D. (2005). Systemic lupus erythematosus in a multiethnic US Cohort (LUMINA). XXX: association between C-reactive protein (CRP) gene polymorphisms and vascular events. *Rheumatology (Oxford)*, 44(7), 864-868.
- Szekanecz Z., Shoenfeld Y. (2004) Lupus and cardiovascular disease: the facts *Lupus*, 15:3-10
- Szekanecz, Z., Szucs, G., Szanto, S., & Koch, A. E. (2006). Chemokines in rheumatic diseases. *Curr Drug Targets*, 7(1), 91-102.
- Thomas, G. N., Tam, L. S., Tomlinson, B., & Li, E. K. (2002). Accelerated atherosclerosis in patients with systemic lupus erythematosus: a review of the causes and possible prevention. *Hong Kong Med J*, 8(1), 26-32.
- Thompson, T., Sutton-Tyrrell, K., Wildman, R. P., Kao, A., Fitzgerald, S. G., Shook, B., Tracy, R. P., Kuller, L. H., Brockwell, S., & Manzi, S. (2008). Progression of carotid intima-media thickness and plaque in women with systemic lupus erythematosus. *Arthritis Rheum*, 58(3), 835-842.

- Tincani, A., Rebaioli, C. B., Taglietti, M., & Shoenfeld, Y. (2006). Heart involvement in systemic lupus erythematosus, anti-phospholipid syndrome and neonatal lupus. *Rheumatology (Oxford)*, 45 Suppl 4, iv8-13.
- Tolozza, S., Urowitz, M. B., & Gladman, D. D. (2007). Should all patients with systemic lupus erythematosus receive cardioprotection with statins? *Nat Clin Pract Rheumatol*, 3(10), 536-537.
- Topaloglu, S., Aras, D., Ergun, K., Altay, H., Alyan, O., & Akgul, A. (2006). Systemic lupus erythematosus: an unusual cause of cardiac tamponade in a young man. *Eur J Echocardiogr*, 7(6), 460-462.
- Tripi, L. M., Manzi, S., Chen, Q., Kenney, M., Shaw, P., Kao, A., Bontempo, F., Kammerer, C., & Kamboh, M. I. (2006). Relationship of serum paraoxonase 1 activity and paraoxonase 1 genotype to risk of systemic lupus erythematosus. *Arthritis Rheum*, 54(6), 1928-1939.
- Tsimikas, S., Brilakis, E. S., Miller, E. R., McConnell, J. P., Lennon, R. J., Kornman, K. S., Witztum, J. L., & Berger, P. B. (2005). Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med*, 353(1), 46-57.
- Turiel, M., Peretti, R., Sarzi-Puttini, P., Atzeni, F., & Doria, A. (2005). Cardiac imaging techniques in systemic autoimmune diseases. *Lupus*, 14(9), 727-731.
- Uchida, T., Inoue, T., Kamishirado, H., Nakata, T., Sakai, Y., Takayanagi, K., & Morooka, S. (2001). Unusual coronary artery aneurysm and acute myocardial infarction in a middle-aged man with systemic lupus erythematosus. *Am J Med Sci*, 322(3), 163-165.
- Urowitz, M. B., Bookman, A. A., Koehler, B. E., Gordon, D. A., Smythe, H. A., & Ogryzlo, M. A. (1976). The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med*, 60(2), 221-225.
- Urowitz, M. B., Kagal, A., Rahman, P., & Gladman, D. D. (2002). Role of specialty care in the management of patients with systemic lupus erythematosus. *J Rheumatol*, 29(6), 1207-1210.
- Urowitz, M. B., Ibanez, D., & Gladman, D. D. (2007). Atherosclerotic vascular events in a single large lupus cohort: prevalence and risk factors. *J Rheumatol*, 34(1), 70-75.
- van der Laan-Baalbergen, N. E., Mollema, S. A., Kritikos, H., Schoe, A., Huizinga, T. W., Bax, J. J., Boumpas, D. T., & van Laar, J. M. (2009). Heart failure as presenting manifestation of cardiac involvement in systemic lupus erythematosus. *Neth J Med*, 67(9), 295-301.
- Veres, K., Lakos, G., Kerényi, A., Szekaneicz, Z., Szegedi, G., Shoenfeld, Y., & Soltesz, P. (2004). Antiphospholipid antibodies in acute coronary syndrome. *Lupus*, 13(6), 423-427.
- Von Feldt, J. M. (2008). Premature atherosclerotic cardiovascular disease and systemic lupus erythematosus from bedside to bench. *Bull NYU Hosp Jt Dis*, 66(3), 184-187.
- Wallace, D. J. (1987). Does hydroxychloroquine sulfate prevent clot formation in systemic lupus erythematosus? *Arthritis Rheum*, 30(12), 1435-1436.
- Wallace, D. J., Metzger, A. L., Stecher, V. J., Turnbull, B. A., & Kern, P. A. (1990). Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. *Am J Med*, 89(3), 322-326.

- Wijetunga, M., & Rockson, S. (2002). Myocarditis in systemic lupus erythematosus. *Am J Med*, 113(5), 419-423.
- Wilson, V. E., Eck, S. L., & Bates, E. R. (1992). Evaluation and treatment of acute myocardial infarction complicating systemic lupus erythematosus. *Chest*, 101(2), 420-424.



Systemic Lupus Erythematosus

Edited by Dr Hani Almoallim

ISBN 978-953-51-0266-3

Hard cover, 554 pages

Publisher InTech

Published online 21, March, 2012

Published in print edition March, 2012

This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

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Sultana Abdulaziz, Yahya AlGhamdi, Mohammed Samannodi and Mohammed Shabrawishi (2012). Cardiovascular Involvement in Systemic Lupus Erythematosus, Systemic Lupus Erythematosus, Dr Hani Almoallim (Ed.), ISBN: 978-953-51-0266-3, InTech, Available from:
<http://www.intechopen.com/books/systemic-lupus-erythematosus/cardiovascular-involvement-in-systemic-lupus-erythematosus>

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