6

Atherogenesis and Vascular Disease in SLE

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1. Introduction

SLE is the classical model of a chronic multi-systemic immune-mediated inflammatory disease. It affects mainly young women, a subgroup of the general population usually free of cardiovascular risk. Although survival rates have improved dramatically, mainly due to early diagnosis, improved treatment, and better management of complications, death rates for patients with SLE remain 3 to 5 times higher than in the general population (Haque & Bruce, 2009). Nevertheless, whilst the 5-year survival of SLE was below 50% in the 1950s, it is nowadays above 90% (Nikpour et al., 2005).

Atherosclerosis in SLE is a highly complex process with autoimmunity, local and systemic inflammation, and endothelial dysfunction playing critical roles in its initiation and propagation. In the particular case of SLE, the extremely intricate immune system deregulation involving all types of immune cells up to an increased autoantibody production seems to play a major role for the accelerated atheroma formation found in these patients.

Cardiovascular events are now the major cause of morbidity and mortality in SLE. The acceptance of the importance of vascular risk in this context came from the description of a bimodal mortality pattern (Urowitz et al., 1976), with the early peak (within 1 year of diagnosis) as a consequence of active lupus and its complications, and the later peak (more than 5 years after diagnosis) mainly attributable to atherosclerosis. SLE is now considered to be a coronary heart disease-risk equivalent, mainly due to accelerated atherosclerosis (Aranow & Ginzler, 2000; Bjornadal et al., 2004; Manzi et al., 1997; Esdaile et al., 2001; Fischer et al. 2004; Roman et al., 2003; Ward, 1999). This can be especially relevant in young women, where up to a 50-fold increase in cardiovascular risk over age and gender-matched controls has been reported (Manzi et al., 1997). In fact, the majority of those women were aged less than 55 years at the time of their first cardiac event.

Framingham risk factors do not explain entirely the atherosclerotic burden found in patients with SLE. Furthermore, traditional cardiovascular risk factors seem to be less important predictors of cardiovascular events than the activity of lupus (Esdaile et al., 2001). (see table 1).

The direct relation between conventional and SLE-related risk factors and the actual incidence of events has not been easy to establish for different reasons: most patients with

SLE are young or middle-age women, for whom the background rate of cardiovascular disease is low, SLE cohorts are small, the number of observed coronary heart disease events is also reduced, and may not provide statistical power for testing their associations with hypothetical SLE-specific risk factors (Karp et al., 2008). This is the main reason why recent studies are considering surrogate markers of cardiovascular risk, such as the presence of carotid plaques, coronary artery calcification and vascular stiffness.

TRADITIONAL RISK FACTORS	INFLAMMATION-RELATED RISK FACTORS	SLE-RELATED RISK FACTORS
Genetics Gender Post-menopausal status Hypertension Dyslipidemia Diabetes mellitus Smoking Obesity Homocysteine Sedentary life-style	Vascular endothelial growth factor Monocyte chemoattractant protein-1 TNF-α, IL-1, IL-6 VCAM-1, ICAM-1 Matrix –degrading proteases Acute phase reactants Vascular endothelial growth factor Monocyte chemoattractant protein-1 TNF-α, IL-1, IL-6 VCAM-1, ICAM-1 Matrix –degrading proteases	Duration of disease Disease activity Disease damage Corticosteroids Auto-antibodies Complement activation Lupus nephritis Increased oxidative stress

Table 1. Proposed cardiovascular risk factors in SLE

Both SLE-specific and non-specific mechanisms have been proposed to play a prominent role in the induction of premature vascular damage, but the exact etiology remains unclear. Chronic inflammation is a very appellative contributor for atherosclerosis, since the pathogenesis of the latter is, in part, mediated by inflammation (Ross, 1999).
A potential confounding factor is that clinically active lupus may also manifest itself with vascular inflammation and thrombosis in any vascular territory. However, when a significant large population is considered, premature vascular disease in SLE is not, as previously thought, just attributable to vasculitis. Actually, it presents mostly as premature atherosclerosis (Bacon et al., 2002; Ward, 1999), both clinically and histologically. Many authors believe that the rapid and progressive nature of vascular injury in patients with SLE makes this population ideal for the identification of mechanisms involved in general atherosclerosis and vascular damage.
This chapter aims at elucidating why patients with SLE are at high risk for cardiovascular events, what different types of vascular conditions may be more commonly found, and what treatments are more likely to help overcome such burden.

2. Burden of disease

Despite the fact that the overall survival of patients with SLE has reached over 90% in recent decades, the long term survival rate has not changed since the 1980s (Petri, 2002). SLE patients have mortality rates of 5-10% at 5 years and 15-30% at 10 years (Abu-Shakra et al., 1995; Jacobsen et al., 1998; Ståhl-Hallengren et al., 2000; Uramoto et al., 1999). This is particularly

overwhelming in patients aged less than 55 years (Abu-Shakra et al., 1995). After the identification of the bimodal pattern of mortality in SLE, a more recent uptade from the Toronto group (Nikpour, 2005) showed that sudden death, congestive heart failure and vascular events are responsible for nearly 30% of late deaths in their SLE cohort. Currently, cardiovascular disease alone accounts for 20 to 30 % of deaths in patients with SLE (Rubin et al., 1985). Even with all-cause mortality declining during the last 20 years the risk of cardiovascular death remains unchanged. With the advent of more potent immunosuppressive and anti-inflammatory treatments, it is likely that the contribution of cardiovascular disease to morbidity and mortality in these patients will increase even further.

Using myocardial perfusion scintigraphy, subclinical coronary atherosclerosis can be present in 28-38% of patients with SLE (Manger et al., 2003; Sella et al., 2003) and the prevalence of symptomatic coronary heart disease (as defined by angina and myocardial infarction) ranges from 6,6% to 20% (Gladman & Urowitz, 1987; Jonsson et al., 1989; Manzi et al., 1997) . Women with SLE in the 35-44 year age group are over 50 times more likely to have a myocardial infarction than women of similar age in the Framingham Offspring Study (Manzi et al., 1997). The mean age at a first coronary event is 49 years in patients with SLE compared with 65-74 years in the general population, as the risk of development of coronary heart disease in the first decade after diagnosis is approximately 12% (Bruce et al., 1999).

There are significant racial disparities regarding age at the time of first hospital admission for a cardiovascular event and cardiovascular-related hospitalization resulting in death in patients with SLE (Scalzi et al., 2010). African-origin, in particular, is associated in an independent fashion with a worsened probability of survival.

The outcomes of hospitalization for acute myocardial infarction were thought to be identical between patients with and without SLE, despite women with SLE being less likely to undergo coronary artery bypass grafting (Ward, 2004). Whether this is due to a decreased need for the procedure or whether reflects a decreased referral or reduced access to the surgery, is not established. More recently it has been recognized that, like diabetes mellitus, SLE increases the risk of poor outcomes after acute myocardial infarction, and these patients should be considered for aggressive treatment. In fact, the risk for prolonged hospitalization is even higher for patients with SLE (OR 1.48, 95% CI 1.32-1.79) compared to those with diabetes mellitus (OR 1.30, 95% CI 1.28-1.32) (Shah et al., 2009).

Cerebrovascular disease has been identified in 2-15% of patients with SLE (Hermosillo-Romo & Brey, 2002; Manzi et al., 1999; Mok et al., 2001; Sanna et al., 2003), with a reported 2-10 times higher risk for stroke SLE (Jonsson et al., 1989; Manzi et al., 1997; Ward, 1999). A recent prospective study showed that the cumulative incidence of arterial thromboembolism in new-onset Caucasian SLE patients is 5,1%, with ischemic stroke and transient ischemic attack comprising 65% of them (Mok et al., 2005) . Cardiovascular risk is even higher in lupus patients who also have secondary antiphospholipid syndrome (APS), due to the additive effects of SLE- and APS-related risk factors. In fact, as APS is also related to accelerated atherosclerosis, it may be difficult to differentiate between SLE- and APS-associated risk factors in these patients.

3. Vascular disease in systemic lupus erythematosus

3.1 Atherosclerosis

3.1.1 Epidemiology

In cross-sectional studies, approximately one-third of patients with SLE has evidence of subclinical atheroma plaques in the carotid or coronary arteries (Asunuma et al., 2003) and

autopsy findings have showed an even higher prevalence of subclinical atherosclerosis (Bulkley & Roberts, 1975). More than 20% of SLE patients who had been on steroids for more than one year before death had a 50% occlusion of at least one major coronary artery. In a cohort of women with SLE, in whom 15% had already a cardiovascular event, 40% had at least one focal carotid artery plaque, a higher frequency than would be expected among healthy women (Manzi et al., 1999). Not surprinsingly, the common carotid intima-media thickness (IMT) of patients with a history of cardiovascular disease is greater than that of SLE patients who had no such history and of healthy volunteers controls (Svenungsson et al., 2001). Using photon emission computed tomography (SPECT) and dual isotope myocardial perfusion imaging (DIMPI), 40% of all women with SLE and 35% of women with SLE and no history of coronary artery disease had abnormalities in myocardial perfusion, reinforcing the idea of a high prevalence of early coronary artery disease (Bruce et al., 2000). Also, coronary-artery calcification, as detected by electron-beam computed tomography (Roman et al., 2003), occurs more frequently and at a younger age in patients with SLE than in healthy controls. Aortic stiffness overall and at any level of the aortic artery was higher in patients with SLE than in controls, even after adjusting for age (Roldan et al., 2010). Furthermore, increased aortic stiffness seems to be an early manifestation of lupus vasculopathy that seems to precede the development of hypertension and atherosclerosis. Whether we consider the SLE context or not, better biomarkers for measuring disease burden are needed. They should be non-invasive, have a good sensitivity and specificity, predict disease in asymptomatic individuals and be available for widespread application.
In clinical practice, diagnosis of atherosclerosis is usually made after the presence of symptoms. Pre-symptomatic screening could identify subclinical disease, allowing for a more aggressive treatment of the different atherothrombotic risk factors.

3.1.2 Atheroma formation

Atherosclerosis is not an age-related process with passive accumulation of lipids in the vessel wall. It must be understood as a dynamic and complex biochemical and anatomical process. It is characterized by changes in lipoprotein metabolism, activation of the immune system and consequent proliferation of smooth-muscle cells, atheroma formation and arterial narrowing. In atheroma formation, inflammation and autoimmunity are at the forefront of the initiation, progression, and rupture of the plaque (Libby et al., 2010; van Leuven et al., 2008). Patients suffering from chronic inflammatory diseases have accelerated atherosclerosis, and the high level of inflammation to which patients with auto-immune diseases are exposed may induce and accelerate endothelial cell injury. Furthermore, biomechanic shear forces enhanced by classic cardiovascular risk factors, such as hypertension, hypercholesterolemia, diabetes and smoking are known to contribute to endothelium dysfunction (Ando & Yamamoto, 2011). In fact, the earliest manifestation of atherothrombosis can be the result of a single disturbance on the physiologic pattern of blood flow at an arterial bending on bifurcation site.
Endothelium regulates anti-inflammatory, mitogenic and contractility activities of the vessel wall; also, it has a role in the the hemostatic process within the vessel lumen. A dysfunctional endothelium is characterized by an increase in oxidative stress. It facilitates oxidation, the uptake of circulating lipoproteins by monocytes, and the migration of these cells to the vessel wall, resulting in the proliferation of smooth muscle cells. The expression of adhesion molecules (such as ICAM and VCAM) induces the binding of monocytes to the endothelial wall (Lusis, 2000). This, when submitted to shear stress

forces is also susceptible to permeation and subendothelial accumulation of apolipoprotein-B-containing lipoproteins, such as low density lipoproteins (LDL) and remnant lipoproteins, that become targets for oxidative and enzymatic attack. After monocyte-endothelial binding takes place, the blood cells are internalized and differentiated into macrophages. Retained pro-atherogenic LDL leads to an enhanced selective leukocyte recruitment and attachment to the endothelial layer, further contributing to their transmigration across the endothelium into the intima. Lipoprotein uptake promotes the accumulation of lipid droplets in the cytoplasm of the macrophages, transforming them into foam cells. The consequent inflammatory response leads to the recruitment of more monocytes, T cells, mast cells and neutrophiles. A fibrous cap is produced by collagen secreting myofibroblasts that populate the intima, and the developing lesion is contained, most of the times, by a fibrous cap. At the beginning, the atherosclerotic lesions are asymptomatic and not at risk for rupture and induction of thrombosis. Atheroma lesions submitted to a chronic inflammatory state will become unstable and may result in an acute vascular event (Virmani et al., 2002). Within those plaques, apoptotic macrophages will suffer necrosis and perpetuate inflammation, with the formation of necrotic cores. These vulnerable or unstable plaques may rupture, exposing pro-coagulant and pro-thrombogenic molecules into the intima and initiating platelet activation and aggregation. This, in turn, will lead to thrombosis and to the clinical manifestation of atherothrombotic disease.

Inflammation plays a major role during all stages of atherosclerosis: endothelial dysfunction, endothelial and cytokine activation, recruitment of inflammatory cells, macrophage uptake of oxidized low-density lipoprotein (oxLDL), development of fatty streaks and fibrous plaque, and finally plaque rupture. Being so, it becomes obvious why SLE and atherosclerosis are so closely related.

3.1.3 Lipids and humoral response towards lipoproteins

Lipid abnormalities are one of the major contributors for atherosclerosis in SLE and different patterns of dyslipoproteinemia have been reported in this disease (Ilowite et al., 1988; Svenungsson et al., 2003). Dyslipoproteinemia in active lupus is characterized by depressed high density lipoprotein cholesterol and apolipoprotein A1 (ApoA1) with elevated very low density lipoprotein cholesterol (VLDL) and triglyceride; on the other hand, the dyslipoproteinemia associated with corticosteroid treatment is characterized by increased total cholesterol, VLDL, and triglycerides. The pattern of dyslipoproteinemia typical of SLE is closely related to disease activity. An enhanced activity in the TNFalpha/soluble TNF-receptor system seems to be an important underlying factor (Svenungsson et al., 2003).

Oxidative stress is also a key factor in atherogenesis, and it is increased in patients with SLE. Interactions between anticardiolipin (aCL) antibodies and anti-oxidant endothelial cells antibodies with the production of pro-oxidant substances suggestes that the interactive mechanisms linking plasma lipoproteins, the immune system, and the endothelium are one of the missing links that can unveil atheroma plaque formation in SLE. Oxidation profile in SLE is reflection of a pro-oxidant status and the presence of aCL antibodies is just one of the potential contributors. A direct effect of aCL antibodies with endothelial cells (inducing inducible nitric oxide synthase expression) leads to an enhanced peroxynitrite synthesis, a pro-oxidant substance, associated with vascular dysfunction and atherogenesis (Delgado Alves et al., 2005).

The primary lipid components involved in atherosclerosis are lipoproteins. Among these, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) assume a central role. HDL are thought to have an anti-atherothrombogenic effect by stimulating endothelial nitric oxide and inhibiting oxidative stress and inflammation (Yuhanna et al., 2001), thus preventing LDL oxidation. LDL is the most pro-atherogenic lipoprotein, due to its ability to capture free radicals becoming itself a powerful pro-oxidant. HDL-associated ApoA1 has known anti-inflammatory properties (Ashby et al., 1998; Hyka et al., 2001) by promoting reverse cholesterol transport from macrophages *in vivo* as well as by blocking contact mediated activation of monocytes by T lymphocytes. Its anti-atherosclerotic actions is also associated with the stabilization of paraoxonase (James & Deakin, 2000). Paraoxonase is an anti-oxidant enzyme that prevents the formation of lipid peroxidation products, such as oxLDL. Higher paraoxonase activity is associated with a lower incidence of cardiovascular events (Soran et al., 2009).

HDL has several other antiatherogenic properties, including the transport of cholesterol from peripheral tissues to the liver. The concept that macrophage-cholesterol efflux has a significant role in cardiovascular disease prevention was recently suggested by the finding of a strong inverse association between HDL-mediated cholesterol efflux from macrophages, carotid intima media thickness (IMT) and the likelihood of coronary heart disease (Khera et al., 2011). These effects were shown to be independent of HDL-cholesterol level. Nevertheless, low levels of HDL increase the cholesterol burden and macrophage-driven inflammation, being strongly associated with the risk of coronary artery disease. Another condition that increases that risk involves the conversion of HDL to a dysfunctional form that is no longer cardioprotective (Barter et al., 2004), but instead acquire a pro-inflammatory and pro-oxidant phenotype promoting atherosclerosis (Delgado Alves et al., 2002, 2009). Regardless of all these data, the underlying mechanisms are still unclear, and no widely accepted methods for determining HDL function have been recognized. Other possible mechanisms for HDL dysfunction may be the increased glycation with the consequent ApoA1 multimerization and decreased phospholipid content (Parker & Cho, 2011). This proinflammatory form of HDL (piHDL) has been described in SLE (Navab et al., 2001) High levels of piHDL increases the risk of developing subclinical atherosclerosis in SLE (MacMahon et al., 2009).

A new concept has merged recently that might account for the higher risk of atherosclerosis in SLE: the humoral response towards HDL. It has been confirmed the presence of IgG antibodies towards HDL and its main protein component ApoA1 in patients with SLE. By interfering with the anti-atherogenic properties of HDL, anti-HDL and ApoA1 antibodies enhance oxidative stress and the consequent SLE-related atherosclerotic lesions. Anti-HDL antibodies are associated with decreased paraoxonase activity, increased biomarkers of endothelial dysfunction (nitric oxide, adhesion molecules VCAM-1 and ICAM-1), reduced total antioxidant capacity, and also increased disease-related damage and activity (Batuca et al., 2009). Both anti-HDL and anti-apolipoprotein A1 antibodies cross react with aCL. Theoretically, anti-HDL and anti-ApoA1 antibodies that cross react with aCL antibodies may contribute to endothelial dysfunction by favouring the oxidation of LDL.

Anti-ApoA1 antibodies have also been described in acute coronary syndromes (Vuilleumier et al., 2008), and they be potential markers of plaque instability (Montecucco et al., 2011).

LDL is the major cholesterol carrying lipoprotein in plasma and may exist in different forms. OxLDL injures cells in artery walls, and promotes atheroma formation (Colles et al., 2001; Hessler et al., 1979). Small dense LDL, when compared with its larger, normal-size

counterpart, is more easily oxidized, has a higher affinity for extracellular matrix, and is subject to a higher degree of retention in the arterial wall (Berneis & Krauss, 2002; Hurt-Camejo et al., 2001; Packard & Sheperd, 1997). Also, smaller LDL has reduced binding to LDL receptors (Chapman et al., 1998) and a longer "half-life". These facts may lead to a greater degree of structural modification, which further increases its atherogenic profile.
In SLE, antibodies to oxidized LDL (anti-oxLDL) have been demonstrated in up to one half of patients with SLE (Romero et al., 1998). Also, anti-oxLDL antibody levels correlate with complement activation, disease activity scores, anti-double-stranded DNA antibody titres (Gómez-Zumaquero et al., 2004) and were found to facilitate the formation of foam cells(Matsuura et al., 2006)

3.1.4 Inflammation and acute response

It is already established that inflammation plays a pivotal role in the pathogenesis of atherosclerosis. It mediates several of the stages of atheroma development from initial leukocyte recruitment to eventual rupture of the unstable atherosclerotic plaque. SLE is characterized by a low-grade persistent pro-inflammatory state, present not only during flares but also during stable disease. The chronic burden of activated inflammatory mediators may have a considerable impact on endothelial cell function and blood coagulation. Several inflammatory circulating intermediates in SLE have been identified as highly atherogenic, such as IL-1, IL-6, IL-18, monocyte chemotatic protein 1, interferon γ and TNFα, among others (Asanuma et al., 2006; Blake &Ridker, 2001; Aringer & Smolen, 2004).
C-Reactive protein (CRP) is an acute phase protein that plays a major role in the regulation of the inflammatory response. It has been implicated in the promotion of both leukocyte adhesion and migration and also in vascular endothelial dysfunction by inducing adhesion molecules, chemokines and cytokines(Pasceri et al., 2000, 2001). Levels of C-reactive protein (CRP) have been shown to be predictive of cardiovascular disease in the general population (Ridker et al., 2002). High-sensitivity CRP and ICAM-1 have been associated with increased coronary artery calcification in SLE patients (Kao et al., 2008). The interaction of anti-monomeric CRP with monomeric CRP in blood vessel walls may also contribute to development of cardiovascular disease in SLE (O'Neill et al., 2007).
As compared with other auto-immune diseases, such as rheumatoid arthritis, the magnitude of CRP elevation is less important. It has been proposed that the relatively low CRP levels in SLE patients can be explained by increased clearance or decreased production of this protein. Autoantibodies to CRP in SLE patients support its increased clearance (Bell et al, 1998; Sjowall et al, 2004); however, the plasma clearance rate of CRP is the same in patients with active lupus and normal individuals, which makes this hypothesis less likely (Vigushin et al, 1993).

3.1.5 Insulin resistance and the metabolic syndrome

The metabolic syndrome is a new defined cluster of risk factors associated with increased insulin resistance, higher risk of developing type II diabetes mellitus and cardio and cerebrovascular events. It is an independent predictor of cardiovascular morbidity and mortality. These risk factors include abdominal obesity, pro-atherogenic dyslipidemia and elevated blood pressure. Even though individually these abnormalities may contribute little, as a risk-factor cluster it is very important and aggressive treatment should be considered in these patients. It is estimated that this syndrome may affect 20-25% of the overall population in the United States and the prevalence increases with age (Ford et al., 2002).

Insulin resistance is characterized by an impaired response to insulin in several insulin-sensitive tissue, such as muscle, liver, fat and endothelium (Simonson et al., 2005). Insulin has anti-inflammatory properties, mainly due to its ability to suppress several proinflammatory transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) , early growth response protein 1 (Egr-1) and activator protein 1 (AP-1) (Aliada et al., 2002). Insulin resistance is a main contributor to the increased cardiovascular risk attributed to the metabolic syndrome (Hanley et al., 2002). There is a link between high levels of proinflammatory cytokines and cardiovascular disease through metabolic pathways. The exact mechanisms linking insulin resistance and inflammation are not fully established. A possible candidate is TNF- α. It is over-expressed in the adipose tissues of animal models of obesity (Hotamisligi et al., 1993). Adipose tissue act as an endocrine secretory gland, producing several inflammatory mediators, responsible for a pro-inflammatory state and thus to an increased cardiovascular risk (Després & Lemieux, 2006).
Tumor necrosis factor-α (TNF-α), IL-1β, IL-4, IL-6, IL-11, Interferon-γ (INF-γ), acting on sensitive adipocytes, can lead to the activation of inflammatory signaling cascades (Rajala & Sherer, 2003). As a response to fat activation, there is enhanced expression and secretion of several acute phase reactants and also mediators of inflammation, such as TNF-α, IL-1β, IL-6, IL-8, IL- 10, prostaglandin E2 (PGE2). Leptin, adiponectin, and resistin (Fain et al., 2004) can perpetuate in the highly pro-inflammatory state.
SLE is associated with an increased prevalence of the metabolic syndrome (El-Magdami et al., 2006). The frequency of metabolic syndrome amongst patients with SLE varies from 16,7% in Mexico(Zonana-Nacah e tal., 2008), 28,6 % in Argentina to 29,4 % in USA (Chung et al., 2007) and 32,1 % in Brazil (Telles et al., 2010), with other cohorts showing similar results. Other metabolic-associated changes such as insulin resistance, premature menopause, renal impairment and high triglyceridemia also occur more frequently in SLE. Controversy still remains regarding the exact role of metabolic syndrome in predicting long-term risk for coronary heart disease in SLE. The major benefit in recognising this syndrome in the context of SLE is related to the identification of patients more in need for lifestyle interventions and specific therapeutic approach.
There is no clear association between treatment with steroids and the development of metabolic syndrome (Telles et al., 2007. However, prednisone in dosages higher than 10 mg/ day and high dosages of intravenous methylprednisone has been previously associated with this condition (Négron et al., 2008). These findings are still not definitive as they can be a reflection of lupus activity and severity. In fact, low-dose steroids may still be of value, due to its anti-inflammatory effects.

3.1.6 Traditional risk factors for cardiovascular disease in SLE

A patient with SLE and cardiovascular disease has on average one less traditional risk factor than people in the general population with a similar cardiovascular condition (Bruce, 2005; Urowitz et al., 2007) and the baseline 10-year coronary heart disease and stroke risk (after adjusting for Framingham score) for all patients with SLE is 7.5–17-fold higher (Esdaile et al., 2001). This is one of the reasons why the relative importance of the individual traditional risk factors differs between patients with SLE and the general population.

Hypertension

Hypertension is a predictor of mortality and vascular events in SLE (Petri et al., 1992; Rahman et al., 2000). It is more common than in the general population with a relative risk

of 2.59 (95% CI 1.79–3.75) (Bruce et al., 2003), independently of whatever treatment for SLE is being administred.

Smoking

Smoking, a well known risk factor for atherosclerosis, is not more frequent in patients with SLE than in the general population (RR 0.86, 95% CI 0.59–1.24) (Boyer et al., 2011), but in the Systemic Lupus International Collaborating Clinics registry (SLICC) (Urowitz et al., 2008) the prevalence of smokers increased from 13.7% at baseline to 18.7%.

Dyslipidemia

Hpercholesterolemia in lupus patients is associated with an 18-fold increased risk of myocardial infarction as compared with the general population (Fischer et al., 2004).

Body composition and low physical exercise

Patients with lupus are more likely to have a sedentary lifestyle, with consequent obesity and hypercholesterolemia (Petri et al., 1992). Low physical activity is associated with increased subclinical atherosclerosis and proinflammatory HDL levels in patients with SLE. Despite the common presence of fatigue as a symptom of the disease, there is reason to believe that exercise should be included in the rehabilitation of patients with mild to moderate SLE (Yuen et al., 2011). Exercise, if well tolerated, may reduce the risk of atherosclerosis in SLE (Volkmann et al., 2010).

3.1.7 Other risk factors

Treatment of SLE and its most common co-morbidities has become more and more complex with drug interactions and side effects becoming a very important issue. Apart from the classical complications of steroid and immunosuppressive treatment, new associations between drugs and clinical adverse effects have been identified. Azathioprine, as an example, was associated with arterial events (hazard ratio of 1.45 (95% CI 1.21–10.4) (Toloza et al., 2004) and with the presence of carotid plaques (Ahmad et al., 2004). Although we should keep these results in mind, the fact is that azathioprine is used in more active disease and it may be just a surrogate for more severe inflammation.

Hyperhomocysteinemia is a well known risk factor for cardiovascular disease and it is a possible marker of atherosclerosis progression and more-active lupus (Bultink et al., 2005; Kianai et al., 2007; Roman et al., 2007). It decreases the availability of endothelial cell-derived nitric oxide, impairs endothelial-dependent vasodilatation, induces oxidative stress, and increases the risk of thrombosis (Maron & Loscalzo, 2009). Homocystein actions on endothelial cells are partly mediated by asymmetric dimethylarginine (ADMA), an intrinsic inhibitor of nitric oxide synthase (Stuhlinger et al., 2003). High levels of ADMA have been described in patients with renal and heart failure, diabetes mellitus, hypertension, and acute coronary events and may predict stroke, coronary artery disease, and also cardiovascular-related death (Laier et al. 2008; Wilson et al., 2008). Among patients with SLE, higher ADMA levels are linked to a higher prevalence of cardiovascular disease.

Hyperuricemia correlates with arterial stiffness and inflammation markers in patients with SLE without symptomatic atherosclerotic disease. It has been showed that women with SLE and hyperuricemia have a high risk cardiovascular profile with metabolic syndrome and renal failure.

3.2 Vasculitis

In the absence of clinically significant coronary atherosclerosis, two other major mechanisms of vascular damage may occur: vasculitis and thrombosis.

The prevalence of vasculitis in SLE patients ranges from 11% to 20% (Cardinali et al., 2000; Wisnieki, 2000). Small vessels (both arteries and venules) of the skin are the most commoly involved (Gonzalez-Gay et al., 2005); medium-sized vessel involvement is less frequent (D'Cruz et al., 1993), and large vessel involvement is rare (Goldberger et al., 1992). Although vasculitis presents mainly as cutaneous lesions, the clinical spectrum is wide, and lifethreatening ischemic injury may result from vasculitis of medium-sized vessels in the gastrointestinal, cardiac, pulmonary, or cerebrovascular regions (D'Cruz, 1998).

Coronary vascular damage may be related to coronary arteritis, affecting preferentially small-size coronary arteries (Bulkley & Roberts, 1975) or, rarely, the medium-size coronary arteries (Bonfiglio et al., 1992); and/ or coronary artery thrombosis. Acute myocardial infarction due to coronary arteritis is reported in SLE, although the incidence is very low.

Immune complex deposition and complement activation play important roles in the pathogenesis of vasculitis in general and coronary arteritis in particular. In patients with both SLE and antiphospholipid syndrome, microvascular thrombi of the coronary circulation, with discrete atherosclerosis and vasculitis, have been observed (Brown et al., 1988).

The distinction between atherosclerosis and arteritis is a difficult task, because coronary vasculitis often occurs in the absence of a clinical SLE flare and also with minimal serologic evidence of disease activity (Wilson et al., 1992).

Central nervous system (CNS) vasculitis in the context of SLE is rare, although it has been found in autopsies in SLE in 7-12% of cases (Johnson & Richardson, 1968; Ellis & Verity, 1979).

Stroke (both ischaemic and haemorrhagic) and SLE cerebral vasculopathy are far more frequent. While ischaemic stroke in SLE is strongly associated to antiphospholipid syndrome, atherosclerosis (Bruce, 2005) and Libman-Sacks endocarditis (Moyassaki et al., 2007), factors that contribute to hemorrhagic stroke are less clear.

The predominant pathology finding in CNS vessels in SLE patients is a noninflammatory small vessel vasculopathy involving small arterioles and capillaries. At autopsy, 50% of the patients have cerebral vasculopathy, characterized by hyaline thickening and eosinophilia of the vessel wall, fibrinoid degeneration without vasculitis, and endothelial proliferation, sometimes accompanied by microhemorrhages (Devinsky et al., 1988; Ellison et al. 1993; Hanly et al., 1992).

3.3 Thrombosis

Thrombotic events are reported in 7-12% of patients with SLE (Somers et al., 1999). During the first year of disease, the incidence of both arterial and venous thrombotic events increases. Several reasons have been pointed out, and include aPL antibodies, circulating immune complexes, high levels of disease activity, and chronic inflammation (Manger et al., 2002). When associated with SLE, antiphospholipid syndrome is a relevant predictor of organ damage and death in patients (Ruiz-Irastorza et al., 2004). Anti-cardiolipin (aCL) antibodies, lupus anticoagulant (LAC) and anti-beta2-glycoprotein 1 antibodies (anti-B2GPI) are detected in approximately one-third of patients with SLE (Love & Santoro, 1990), especially in the context of the antiphospholipid syndrome. The best predictors for thrombotic events in SLE are persistent aPL antibodies, the presence of LAC (Somers et al., 2002), and high titers of aCL antibodies (Ginsburg et al., 1992).

Not all thrombotic phenomena are associated with the presence of aPL antibodies and some patients may develop venous and arterial thrombosis without aCL positivity. The relevance of traditional and SLE-related thrombotic risk factors in aPL positive patients is still under investigation. Most of the patients with SLE and aPL antibodies who developed thrombosis had other thrombotic risk factors (Erkan et al., 2007). Interestingly, after adjusting for other risk factors, SLE itself remains independently associated with thrombotic events (Bruce, 2005). Thrombosis is frequent in early SLE and is associated with a significant mortality; therefore, the identification of possible modifiable risk factors and the establishment of efficacious strategies of prevention and treatment are vital.

4. Treatment

The impact of cardiovascular disease has been under-recognized in the context of SLE, with limited attention on aggressive management of possible modifiable risk factors. Despite a general awareness of coronary vascular disease in SLE patients, physicians do not address risk factors in a comprehensive fashion. Also, the management of conventional cardiovascular risk factors such as diabetes mellitus, smoking, hypercholesterolemia and hypertension is not at the same level of non-SLE patients. This is reinforced by the fact that recruiting and retaining patients with SLE for clinical trials regarding preventive measures has been proven to be extremely difficult.

It is therefore of great importance to identify in each patient the modifiable risk factors and introduce in clinical practice guidelines to help clinicians reducing long-term cardiovascular morbidity and mortality. In this chapter, we analyze the potential impact of some of the most commonly used drugs in SLE and their effects in the cardiovascular system.

The general approach suggested in the overall population for primary and secondary prophylaxis of vascular disease should be proposed to every patient and should include (table 2):

4.1 Corticosteroids: Are they good or bad for lupus?

Corticosteroids still remain a first line treatment for lupus, despite having numerous detrimental side effects on blood pressure, blood glucose and lipid profile (Manzi et al., 2000). Corticosteroids have a particular deleterious effect on the heart (Bulkley et al., 1975). Prednisone dosage superior to 7,5 mg/d increases insulin levels, a risk factor for cardiovascular disease (Karp et al., 2008) and total cholesterol, triglycerides and apolipoprotein B levels increase significantly with a daily prednisone dose higher than 10 mg (Petri et al., 1992). The estimated 2-year coronary risk for a patient treated with anved an average dosage of 30 mg/day of prednisone for 1 year, is approximately 60% higher than it would be for a patient with the same levels of SLE activity and similar risk factors who received no corticosteroids (Karp et al., 2008).

When compared to a baseline chronic inflammatory status, low dose corticosteroids may exert an anti-inflammatory action which might be beneficial. In fact, such exposure may improve the lipid profile and increase insulin levels, whithout having a negative effect on blood pressure and atherosclerosis. A weak association between low-dose corticosteroids and cardiovascular risk factors has been established, and identified a dose-related trend for increasing major cardiovascular events (Ruyssen-Witrand et al., 2010). Furthermore, subclinical atherosclerosis is correlated with lower mean dose of corticosteroids and lesser immunossupressants (Roman et al., 2003).

Cholesterol	1. Screening: fasting lipid profile every year; 2. For LDL cholesterol <2.6 mmol/l: no treatment; 3. For LDL cholesterol 2.6–3.4 mmol/l: therapeutic lifestyle changes. 4. Consider statins when LDL is >3.4 mmol/l with or without other risk factors; or when LDL is persistently >2.6 mmol/l despite therapeutic lifestyle changes.
Hypertension	1. Blood pressure assessments at every visit to the outpatients clinic; 2. Ideal target is defined as blood pressure at <130mmHg systolic and <80mmHg diastolic. 3. If elevated blood pressure (>140 mmHg systolic or >90mmHg diastolic): lifestyle modification.; 4. If, despite previous measures, the blood pressure is persistently found to be elevated: start antihypertensive medication.
Diabetes mellitus	1. Regular testing for diabetes (1-2 /year); 2. In patients with a fasting glucose ≥6.1 mmol/l: glucose tolerance test and lifestyle changes; 3. Referral to a specialist in diabetes.
Weight control	1. Screening for obesity; 2. Lifestyle changes, exercise programmes and behavioral support; 3. If, despite efforts, obesity remains, refer to drug/ bariatric surgery by a multidisciplinary team.

Table 2. Summary of some therapeutic interventions.

There are some important limitations in addressing the role of steroids in cardiovascular risk. Corticosteroid use is more common in patients with moderate to severe disease (Bruce, 2006) and the duration of exposure to this drug may function as a surrogate for disease duration. Further work is needed to assess if there are doses or regimes of corticosteroid therapy that can optimise their anti-inflammatory effects whilst minimizing their multiple adverse effects.

4.2 Statins

Pleotropic actions of hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors (statins) have been thourougly reported and is now accepted that their benefits go beyond cholesterol lowering and include immunomodulatory and immunossupressive properties. Statins inhibit HMG-CoA reductase, an enzyme that converts HMG-CoA to mevalonate, a fundamental step in cholesterol synthesis. The mevalonate pathway is involved in posttranslational modification of cell-signaling proteins during cell division and maturation, with inhibition of proinflammatory effects. It then promotes anti-inflammatory activities through the direct inhibition/activation of chemokyne, cytokine-, and acute-phase reactant-driven intracellular pathways in several cell types involved in inflammation. Statins modulate the activity of cells involved in both innate and adaptative immune responses, affecting the production of cytokines and cellular adhesion molecules (e.g. ICAM-a, IL-6, TNF-α, IL-1 and selectin levels (Mira & Mañes, 2009) and have an antithrombotic effect by

inhibiting platelet activation (Ferroni et al., 2006). In the general population, statins have shown efficacy in primary and secondary prevention of acute myocardial infarction and stroke (Amarenco et al., 2006; Ridker et al., 2008).
Following the identification of their mechanisms of action, statins became a potential drug for treating SLE patients despite cardiovascular involvement. Low dose rosuvastatin induced a significant reduction in LDL and CRP after 12 months treatment (Mok et al., 2011). In patients with low disease activity, rosuvastatin decreased plasma levels of endothelial activation markers such as P-selectin and VCAM-1. Unexpectedly, in 2011, the results from the Lupus Atherosclerosis Prevention Study (Petri et al., 2011) offered no evidence that atorvastatin could reduce markers of subclinical atherosclerosis or disease activity over 2 years and the anti-inflammatory effects of statins observed in the general population were not replicated in this SLE clinical trial. However, comments were raised regarding the homogeneity of both treatment arms which may limit the final interpretation. Importantly, there was no information about the treatments received by patients during the 2 years follow-up, regarding the use of prednisone, immunosupresive agents and hydroxychloroquine, all of them having a direct effect on inflammation and disease activity and potentially on subclinical atherosclerosis. Hence, the negative results in this clinical trial could be caused by an imbalance in the use of these drugs in both arms, rather than by the lack of efficacy of atorvastatin.

4.3 Low dose salicylic acid

Most of SLE patients with aPL, but without a history of thrombosis, do not receive any preventive therapeutic, while some receive low dose salicylic acid (ASA) (Kamashta, 2000). Prophylactic treatment with ASA in SLE patients may prevent both arterial and venous thrombotic manifestations, especially in patients with positive aPL (Wahl et al., 2000). In fact, ASA decreases the probability of thrombosis in asymptomatic individuals with aPL (Erkan et al., 2002). The use of low-dose ASA has been recommended by the expert committee in the recent European League Against Rheumatism guidelines for the management of SLE (Bertsias et al., 2008).

4.4 Hydroxychloroquine

Hydroxychloroquine is an anti-malarial drug also used to treat SLE, Sjögren's syndrome and other immune mediate diseases. Several mechanisms have been proposed to explain its beneficial effect, which is not fully established. Hydroxychloroquine can inhibit the binding of antiphospholipid antibody–β2-glycoprotein I complexes to phospholipid bilayers (Rand et al., 2008), reverse platelet activation induced by human IgG aPL antibodies (Espinola et al., 2002), and reduce of aPL antibody–induced thrombosis (Edwards et al., 1996). There is no consistent data regarding whether this antithrombotic effect is present both for arterial and venous events.
A beneficial effect on serum lipid levels, including patients taking corticosteroid therapy (Borba et al., 2001; Hodis et al., 1993; Sachet et al., 2007; Tam et al., 2000), was shown by a few observational studies. However, the strenght of evidence supporting a clinically meaningful beneficial effect was rated as low. Also, there is no data supporting any protective effect of this drug on the development of metabolic syndrome (Ruiz-Irastorza et al., 2010).

Regarding the effect of hydroxychloroquine on atherosclerosis, most studies are limited by the low consistency and lack of specific design (Ahmad et al., 2007; Maksimowicz-McKinnon et al, 2006). The effect was not quantified in most cases and the exposure to hydroxychloroquine has been heterogeneously defined, without taking into account the time of exposure or a possible dose effect.
Because of its beneficial effects on reducing SLE activity and mortality, most of the authors recommend hydroxychloroquine for most patients with SLE, starting as soon as the diagnosis is made. Its application for the specific prevention of thrombosis and treatment of atherosclerosis requires validation in future clinical trials.

4.5 B-cell depletion therapy

Rituximab, a drug that had no previously documented lipid-lowering effect, was recently investigated in patients with SLE who had failed standard immunosuppressive therapy (Pego-Reigosa et al., 2010). An increase in HDL cholesterol and a fall in the total cholesterol/HDL ratio and triglyceride levels was documented in a significant proportion of the 12 patients studied. Furthermore, this improvement in lipid profile mirrored a decrease in disease activity; this suggests a positive effect of rituximab related to a reduction in the overall high inflammatory status. Still, larger prospective studies should aim to evaluate if this observed favorable effect contributes to a lower incidence of cardiovascular events.

5. Conclusion

Patients with SLE are at increased risk for cardiovascular complications. Atherosclerosis occurs prematurely in patients with systemic lupus erythematosus and is independent of the traditional risk factors for cardiovascular disease. Premature atherosclerosis has emerged as a leading cause of morbidity and mortality in SLE. Traditional risk factors, such as hypertension, smoking, diabetes, obesity and dyslipidemia are common in SLE but they fail to explain entirely the atherosclerotic burden found in these patients. Increased understanding of the mechanisms underlying vascular damage, plaque formation and stability, and thrombosis, will greatly facilitate the long-term care of patients with lupus. The clinical profile of patients with lupus and atherosclerosis suggests a role for disease-related factors in atherogenesis and underscores the need better trials targeting atherosclerosis in a specific fashion.
An early identification of subclinical atherosclerosis in SLE is warranted to help to identify patients with higher risk to undergo major vascular complications, who might benefit from more aggressive treatment and lifestyle modifications.

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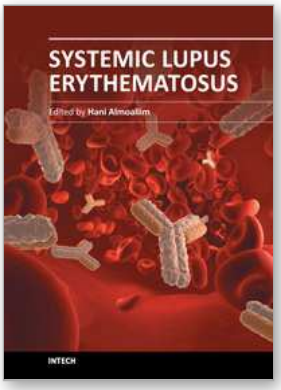

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This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology 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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