Effects of Inflammation on Cholesterol Metabolism: Impact on Systemic Lupus Erythematosus

Allison B. Reiss, MD

Inflammation and dysregulated cholesterol metabolism are key components in the pathogenesis of atherosclerosis. Premature atherosclerosis is a characteristic feature of systemic lupus erythematosus. Although the cellular and molecular mechanisms underlying accelerated atherosclerosis in lupus are not thoroughly understood, inflammation associated with the rheumatic disease state may promote atherosclerosis. Increasing evidence indicates that the systemic inflammatory load in lupus disrupts cholesterol homeostasis, increasing vulnerability to cholesterol accumulation in cells of the artery wall, including macrophages and endothelium. The relationship between the inflammatory state and dyslipidemia in lupus is complex, involving lipoproteins, cholesterol transporters, scavenger receptors, and oxysterols. The impact of lupus on each of these components of the cholesterol flux pathways is discussed. The formation of autoantibodies against epitopes within lipoprotein particles and their controversial role in atherogenesis is addressed.

Introduction
Patients with systemic lupus erythematosus (SLE; lupus) have increased morbidity and mortality resulting from accelerated atherosclerosis [1]. Although the underlying reason for this association is not yet clear, the impact of atherosclerosis on length and quality of life for those with SLE is increasingly apparent as therapeutic interventions have improved prognosis and long-term survival [2]. In SLE, the risk of being affected by atherosclerotic coronary artery disease is four to eight times higher than in the normal population. Lesions may also develop in young premenopausal women, in whom this disease is otherwise rare [3]. Atherosclerosis contributes to approximately 30% of deaths in SLE patients and about 30% of SLE patients have subclinical atherosclerosis [4,5]. The pathogenesis of atherosclerotic vascular disease in SLE cannot be attributed solely to an increased frequency of conventional Framingham risk factors, such as age, sex, total serum cholesterol, diastolic blood pressure, systolic blood pressure, left ventricular hypertrophy, diabetes mellitus, and cigarette smoking. Even after controlling for these factors, other unaccounted factors in SLE patients remain [6]. Corticosteroid therapy, which is common in patients with SLE, may exert direct atherogenic effects on plasma lipoproteins and may also exacerbate hypertension and diabetes. Evidence is accumulating that the chronic activation of the immune system that occurs in lupus may be a major contributing factor to premature atherosclerosis [7]. This fits well with the concept of atherosclerosis as an inflammatory condition, resulting from vascular injury. This review focuses on the potential impact of immune dysregulation in SLE on induction and progression of the atherosclerotic process in the artery wall.

Dyslipidemia and SLE
Atherosclerosis is a multifactorial pathophysiologic condition characterized by endothelial dysfunction, excessive accumulation of lipoprotein-derived cholesterol in the artery wall, chronic inflammation, and extracellular matrix production. These processes ultimately lead to plaque instability, rupture of unstable (inflamed) plaque, and thrombus formation, with the curtailment or obstruction of blood flow through the vessel lumen. Lipoproteins transport lipids, including cholesterol, in the blood. The two most abundant lipoproteins in the plasma are low-density lipoprotein (LDL) and high-density lipoprotein (HDL). The plasma concentration of HDL cholesterol is inversely associated with atherosclerotic disease risk, whereas elevated circulating LDL cholesterol potentiates the risk of atherosclerosis [8].

An SLE-related dyslipidemia pattern has been documented, consisting of elevated triglycerides, lipoprotein(a) (Lp[a]) and very low-density lipoprotein (VLDL) cho-
lesterol, slightly increased LDL, as well as reduced HDL [9–11]. High triglycerides and low HDL are the most frequently observed lipid profile abnormalities in SLE. Total cholesterol levels may be either normal or elevated. SLE dyslipoproteinemias worsen as disease becomes more active so that a marked increase in VLDL and triglyceride levels, as well as a decrease in HDL levels, correlate directly with SLE Disease Activity Index (SLEDAI) scores [9]. Steroid treatment is frequently administered in SLE and can itself alter the lipoprotein pattern by elevating total cholesterol (both HDL and LDL) [12•]. After adjusting for disease activity and duration, as well as medications and other confounders, corticosteroid dosage is associated with significantly higher levels of total serum cholesterol, HDL, LDL, apolipoprotein B (apoB), and triglycerides [12•].

**Triglycerides and Chylomicrons**

Increasing concentrations of circulating triglyceride-rich lipoproteins escalate the risk of atherosclerosis [13]. Plasma levels of triglycerides and VLDL are elevated in lupus [9]. VLDL particles carry endogenously synthesized triglyceride from the liver into plasma, where they undergo lipolysis and are ultimately converted to cholesterol-rich LDL. An additional lipid abnormality that occurs in SLE is decreased lipolytic catabolism and delayed clearance of chylomicrons, apoB, and triglyceride-containing lipoproteins that mediate the transport of dietary lipid [14]. Normally, chylomicrons are cleared rapidly from plasma. The enzyme lipoprotein lipase (LPL) acts to hydrolyze triglycerides from circulating chylomicrons and VLDL into free fatty acids and glycerol. Low LPL activity leads to accumulation of chylomicrons, VLDL, and small dense LDL with high triglycerides and low HDL [15]. Impaired triglyceride metabolism may be attributed to interference with the activity of LPL, possibly due to anti-LPL autoantibodies found at high frequency (40% or more) in SLE [16,17]. The presence of immunoglobulin G (IgG) anti-LPL antibody was associated with higher triglyceride levels and greater disease activity, erythrocyte sedimentation rate, and C-reactive protein (CRP). The cytokine tumor necrotic factor-α (TNF-α) is produced in excess in SLE and circulating levels correlate to disease activity [18]. TNF-α is known for its ability to suppress lipoprotein-lipase activity. This negative effect of TNF-α on lipoprotein lipase may be linked to increased triglycerides and decreased HDL in SLE [10,19]. Levels of TNF-α and of soluble TNF-α receptors measured in SLE patients by enzyme-linked immunosorbent assay correlates with plasma triglyceride concentration [10]. In addition to its effect on LPL, TNF-α may also act directly in the liver to increase de novo hepatic synthesis and VLDL secretion [20].

**LDL Cholesterol, Oxidized LDL, and Atherosclerosis**

LDL cholesterol that has entered the vessel wall through a breach in the endothelial monolayer is susceptible to oxidative damage targeting both the lipid and lipoprotein (apoB100) components. Oxidative or enzymatic modification of LDL takes place preferentially in the subendothelial space of the arterial wall, a sequestered environment with a high concentration of reactive oxygen species (ROS) [21]. Oxidation changes the native properties of LDL so that it is engulfed much faster by the macrophages via the scavenger receptors (ScR) CD36 and ScR-A, encouraging macrophage foam cell transformation [22]. Oxidized LDL (oxLDL) is believed to play an important role in the progression of atherosclerosis. OxLDL decreases gene expression of the endothelial cell nitric oxide synthase, the endothelium-derived relaxing factor that regulates vascular tone and vasomotor function. OxLDL is cytotoxic, induces proinflammatory cytokines and adhesion molecules, and is a potent chemoattractant for monocytes and T lymphocytes [23]. It also stimulates proliferation of macrophages and smooth muscle cells and promotes platelet aggregation. High levels of oxLDL are associated with increased risk of future myocardial infarction, even after adjustment for LDL cholesterol and other established cardiovascular risk factors [24].

LDL is heterogeneous and smaller, denser LDL particles are considered more atherogenic because they are highly susceptible to oxidation and are able to penetrate with ease into the subendothelial space of the vascular wall. Compared with control subjects, a cohort of female SLE patients was found to have an increase in the small, dense, LDL subfraction [11]. OxLDL concentrations negatively correlate with LDL particle size, and hypertriglyceridemia enhances the formation of small dense LDL [25].

Modified lipoproteins, particularly different forms of oxLDL, are highly immunogenic, provoking humoral immune responses and robust autoantibody production in animals and humans that, in turn, result in local immune complex formation [26]. Both plasma and atherosclerotic lesions contain antibodies recognizing various epitopes of oxLDL. Antigen-presenting dendritic cells and macrophages present peptides derived from the oxLDL particle on major histocompatibility complex (MHC) class II molecules for recognition by CD4+ T cells, leading to clonal expansion of oxidized LDL-specific T-cells and autoantibody production [27]. Antibodies against oxLDL, which are predominantly of the IgG isotype, play an important role in atherosclerosis. However, whether they are atherogenic or antiatherogenic remains unclear and a subject of controversy. In multiple animal studies in rabbits and mice, immunization with oxLDL induces formation of antibodies that protect against development of atherosclerosis. The antibodies might have beneficial effects by clearing oxLDL particles from the circulation and preventing them from reentering the arterial wall or by facilitating removal of oxLDL from the vessel wall [28]. However, antibodies might have deleterious effects by promoting the macrophage uptake of oxLDL and lipoprotein immune complexes, resulting in intracellular cholesteryl ester accumulation and the formation of foam cells [29].