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# Dyslipidemia in systemic lupus erythematosus: just another comorbidity?

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ABSTRACT

*Objective:* Among traditional atherosclerotic risk factors, dyslipidemia is believed to decisively affect the long-term prognosis of lupus patients, not only with regard to cardiovascular events but also by influencing other manifestations, such as lupus nephritis. The aim of this study was to review the epidemiology, pathogenesis, evidence for its impact on atherosclerosis manifestations and management of dyslipidemia in lupus patients.
*Methods:* English-restricted MEDLINE database search (Medical Subject Headings: lupus or systemic lupus erythematosus and dyslipidemia or hyperlipidemia).
*Results:* The prevalence of dyslipidemia in systemic lupus erythematosus (SLE) ranges from 36% at diagnosis to 60% or even higher after 3 years, depending on definition. Multiple pathogenetic mechanisms are implicated, including antibodies against lipoprotein lipase and cytokines affecting the balance between pro- and anti-atherogenic lipoproteins. Dyslipidemia has a clear impact on clinical cardiovascular disease and surrogate markers for subclinical atherosclerosis. Moreover, it negatively affects end-organ damage (kidneys and brain). Treatment with statins yielded contradictory results as per minimizing cardiovascular risk.
*Conclusions:* Dyslipidemia is a significant comorbidity of lupus patients with multiple negative effects in the long term. Its treatment represents a modifiable risk factor; prompt and adequate treatment can minimize unnecessary burden in lupus patients, thus reducing hospitalizations and their overall morbidity and mortality.



## Introduction

Premature atherosclerosis and its major sequelae, acute myocardial infarction (AMI), and cerebrovascular disease (CVD), have increasingly been recognized as the leading cause of morbidity and mortality in systemic lupus erythematosus (SLE) patients [1,2]. Acceleration of the atherogenetic process in SLE is related to traditional (i.e., age, arterial hypertension, dyslipidemia, diabetes mellitus, smoking, obesity, and positive family history) and disease-related factors, such as certain immune and inflammatory parameters [3,4]. Among traditional risk factors, dyslipidemia is believed to decisively affect the long-term prognosis of lupus patients not only by increasing cardiovascular (CV) risk per se but also through its negative impact on chronic kidney disease progression and brain damage [5–8]. In this review, the current evidence for dyslipidemia in SLE is summarized in regard to epidemiology, pathogenesis, impact on premature atherosclerosis and other disease manifestations and treatment options.

## Methods

The MEDLINE literature database was searched through PubMed with the following Medical Subject Headings (MeSH): lupus or systemic lupus erythematosus and dyslipidemia or hyperlipidemia. No restriction was applied to the explosion of MeSH in order to include older terms such as hypercholesterolemia,

All authors were involved in the study conception and design, acquisition of data as well as analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Urowitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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hypertriglyceridemia, hyperlipoproteinemias, etc. Search was restricted to English language and publications after 1980 up to present were taken into consideration. Since the primary aim of this review was the description of the overall burden of dyslipidemia on lupus patients, we performed a qualitative synthesis of the available evidence.

## Results

### *Epidemiology and factors influencing dyslipidemia in SLE*

In most studies in SLE patients dyslipidemia refers to elevated total cholesterol (TC), triglycerides (TG) and low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL). By this definition, the prevalence of dyslipidemia in SLE ranges from 36.3%, at the time of diagnosis, to 60% or even higher after 3 years of follow up in the SLICC cohort of 918 patients [9,10].

Other large cohorts showed that decreased HDL is the most common abnormality [11]. Cardoso et al. [12] showed that among 185 Brazilian SLE patients, approximately 48% suffered from hypercholesterolemia, 30% hypertriglyceridemia and 60% both. In Asian lupus patients, dyslipidemia was present in 65.3–84.6% (in particular, elevated TC in 43%, LDL in 26.4%, TG in 44.2%, and low HDL in 26%) [13,14]. Moreover, the prevalence of the metabolic syndrome is estimated at almost one-third (32.1%) of SLE patients, whereas low HDL levels were reported in 61.1% and high TG levels in 29% of those patients [15].

Lupus nephritis patients were shown to have higher TC and TG serum levels than age and sex-matched non-diabetic patients with the same severity of chronic kidney disease [16]. Of note, dyslipidemia (increased TC, TG, and LDL or decreased HDL) was also more prevalent in patients with discoid lupus (compared to healthy individuals) [17].

In pediatric SLE, lipid abnormalities (mainly increased TG and decreased HDL levels) were already present at diagnosis in 63% of children with SLE [18]. These findings were twice as common in the presence of kidney involvement.

Multiple variables have been associated with the increased prevalence of dyslipidemia in SLE. Disease activity (as evaluated by SLE Disease Activity Index, SLEDAI) accounted for low HDL [12,13], 24-h proteinuria and obesity were associated with high TC and LDL [12] as well as disease duration over 3 years and prednisone dose $>$ 30 mg/day [13].

The main lipid abnormalities in various lupus cohorts are presented in the Table.

Besides the basic lipid profile, other lipid biomarkers with, yet, unspecified significance have also been studied. Apolipoprotein E (ApoE) has been found elevated in lupus patients (as compared to normal controls) and was correlated to disease activity [19]. On the contrary, serum apoA1 (a cholesterol transport protein with anti-atherogenic properties) was significantly decreased, probably due to the presence of specific anti-apoA1 antibodies [20–22]. Furthermore, it was demonstrated that low levels of anti-apoB100 antibodies in SLE patients are highly correlated to atherosclerotic cardiovascular events [23]. Nevertheless, no atherogenic (including lipoprotein B, apoC, apoD, apoE, etc.) or atheroprotective lipoprotein (including apo-AI and LpA-I) was associated with subclinical atherosclerosis in SLE [24].

**Table**
The main lipid abnormalities in various lupus cohorts

| Study | Patients | *n* | TC (%) | TG (%) | LDL (%) | HDL (%) |
|---|---|---|---|---|---|---|
| Toloza et al. [11] | South America | 546 | 23.9 | 15 | 22.5 | 81 |
| Cardoso et al. [12] | Brazilian | 185 | 48.1 | 29.7 | 43.8 | 24.3 |
| Wijaya et al. [13] | Indonesia | 77 | 40.3 | 44.2 | 36.4 | 26 |
| Siripaitoon et al. [14] | Thailand | 93 | | | | 9.7 |
| Telles et al. [15] | Brazil | 162 | 19.8 | 29 | 18.5 | 61.1 |
| Tyrrell et al. [18] | Canada (pediatric) | 190 | 20 | 62 | 4 | 24 |

The distinct characteristics of dyslipidemia in SLE are associated with primary abnormalities of lipoprotein metabolism [25]. The so-called "*lupus pattern of dyslipidemia*" includes elevated VLDL and TG and decreased HDL levels and is directly related to disease activity. This pattern is usually detected at disease diagnosis (in untreated patients) [18,25].

In addition, differences regarding the size and volume of certain lipoprotein particles have been described in SLE, although with contradictory results [26,27].

### *Pathogenesis of dyslipidemia in SLE*

#### *The role of autoantibodies*

Pathogenetic mechanisms accounting for the *lupus pattern of dyslipidemia* have not been elucidated; however, lipoprotein lipase (LPL), the main enzyme involved in the lipolysis process, might play a role [28,29]. In lupus patients, LPL activity is impaired, due to delayed removal of chylomicron remnants by the respective liver receptors, resulting in accumulation of chylomicrons and VLDL, and subsequently, increased TG and reduced HDL levels [29,30]. Furthermore, autoantibodies against LPL may further decrease its activity [31,32]. The prevalence of anti-LPL antibodies in SLE was described to be approximately 47%; in addition, anti-dsDNA antibodies were shown to exert anti-LPL activity [32]. In addition, anti-LPL antibodies correlated with high disease activity and increased TG, apoB, and apoE levels, suggesting that the disease-related inflammatory load significantly affects the balance of pro- and anti-atherogenic lipoproteins [32] (Fig.).

Besides some rare cases of extreme hypertriglyceridemia (as a consequence of anti-LPL antibodies) [33], the lupus pattern of dyslipidemia decisively drives LDL oxidation. Hypertriglyceridemia enhances the replacement of cholesterol esters in the core of LDL particles, thus making them more susceptible to oxidation [34]. Oxidized LDL (oxLDL) is considered the main antigenic target of the immune system, as its uptake by the macrophage's scavenger receptors is the initial step to foam cell formation and is elevated in SLE [35]. On the other hand, the natural anti-atherogenic properties of HDL are neutralized in an inflammatory microenvironment [36,37]. In SLE, a significant proportion of HDL is dysfunctional and fails to inhibit LDL oxidation; this proinflammatory HDL was demonstrated to be an independent risk factor for carotid atherosclerosis [38].

Other antibodies have also been implicated in the impaired lipid metabolism in SLE. IgG anti-oxLDL antibodies have been repeatedly described in lupus patients and enhance the accumulation of LDL into the arterial wall, by increasing its uptake through the macrophage Fc receptors [39]. Furthermore, cross-reactions between anti-oxLDL antibodies and anticardiolipin (aCL), anti-HDL and anti-apoA1 antibodies have been reported in SLE [40,41]. These results may partially explain the association of IgG aCL and lupus anticoagulant with low HDL in lupus patients [21,42]. Anti-oxLDL/β2GPI immune complexes have also been described in SLE [43,44], probably representing a compensatory mechanism, as β2GPI binds oxLDL to counteract its inflammatory properties. However, these large complexes are phagocytosed by the macrophages and promote foam cell formation. Of note, these complexes and anti-b2GPI antibodies correlate with elevated TG and reduced HDL levels [44].

#### *Cytokines involved in SLE-related dyslipidemia*

Certain cytokines and soluble mediators, involved in SLE pathogenesis, exert remarkable effects on lipoprotein metabolism.