Mechanisms of dyslipoproteinemias in systemic lupus erythematosus

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Abstract

Autoimmunity and inflammation are associated with marked changes in lipid and lipoprotein metabolism in SLE. Autoantibodies and cytokines are able to modulate lipoprotein lipase (LPL) activity, a key enzyme in lipid metabolism, with a consequent “lupus pattern” of dyslipoproteinemia characterized by elevated levels of very low-density lipoprotein cholesterol (VLDL) and triglycerides (TG) and lower high-density lipoprotein cholesterol (HDL) levels. This pattern favors an enhanced LDL oxidation with a subsequent deleterious foam cell formation. Autoantibodies and immunocomplexes may aggravate this oxidative injury by inducing accumulation and deposition of oxLDL in endothelial cells. Drugs and associated diseases usually magnify the close interaction of these factors and further promote the proatherogenic environment of this disease.

Keywords: *Systemic lupus erythematosus, lipoprotein, dyslipoproteinemia, hyperlipidemia, atherosclerosis, inflammation*

Introduction

Atherosclerosis has been increasingly recognized as an important cause of morbidity and mortality in systemic lupus erythematosus (SLE) (Hahn 2003; Bruce 2005; Frostegard 2005; Shoenfeld et al. 2005) and therefore, understanding the pathogenesis of this process seems important to give lupus patients a better long-term outcome and quality of life. Indeed, these patients are known to have an increased frequency of traditional risk factors such as hypertension, dyslipidemia, obesity and diabetes mellitus (Petri et al. 1992; Bruce et al. 1999; Svenungsson et al. 2001; Bruce 2005). However, it has now become clear that atherosclerosis cannot be entirely explained by Framingham risk factors and may be associated with a combination of both traditional and nontraditional risk factors (Esdaile et al. 2001; Svenungsson et al. 2001; Lee et al. 2006).

Interestingly, immune and inflammatory mechanisms seem to have a role in the pathogenesis of atherosclerotic vascular damage (Ross 1993; Ross 1999; Libby 2002). This raises the exciting possibility that SLE itself may be atherogenic through chronic activation of the immune system and inflammatory

process. In fact, autoantibodies such as antiphospholipid, anti- β 2-glycoprotein I, antioxidized low-density lipoprotein and anti-lipoprotein lipase and elevated inflammatory markers such as C reactive proteins (CRP) and interleukin 6 (IL-6) are common findings of SLE.

It is therefore reasonable to postulate that the interaction of disease associated factors induces specific alterations in lipoprotein metabolism which is aggravated by drugs and associated conditions frequently observed in lupus patients.

The “lupus pattern” of dyslipoproteinemia

SLE is alleged as a classic model of a chronic immune complex-mediated inflammatory disease and probably several conditions detected in this disorder may enhance atherogenesis. Similarly, atherosclerosis is now assumed as a chronic process closely related to inflammation, which plays a pivotal role in the mechanisms of induction and progression of the atherosclerotic process in vessels (Ross 1993; Ross 1999; Libby 2002). It is well known that the acute-phase response promotes an altered hepatic synthesis

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of a wide array of proteins involved in coagulation, in the complement system, and in lipoprotein metabolism (Gabay and Kushner 1999). Therefore, it seems reasonable to accept that inflammatory conditions of the disease itself would induce specific alterations in the lipid profile.

Reinforcing this possibility, sporadic cases of hyperlipoproteinemia type I (Glueck et al. 1969a,b; Pauciullo et al. 1986), and V (Alverson and Chase 1977) preceding SLE have been reported and provide support for the direct involvement of the disease in this process. Subsequently, definitive evidence for primary abnormalities of lipoprotein metabolism due to SLE *per se* was recognized (Ilowite et al. 1988; Borba and Bonfa 1997). The "lupus pattern" of dyslipoproteinemia identified was characterized by elevated levels of very low-density lipoprotein cholesterol (VLDL) and triglycerides (TG), and lower high-density lipoprotein cholesterol (HDL) levels (Ilowite et al. 1988; Borba and Bonfa 1997). Interestingly, activity seems to worsen this dyslipoproteinemia since a striking increase of VLDL and TG levels and decrease of HDL levels were directly correlated with SLEDAI scores (Borba and Bonfa 1997).

It should be emphasized that the most common abnormality in SLE is low HDL levels, which are detected in almost 80% of patients with active disease but also in approximately one-third of inactive patients (Borba and Bonfa 1997). Since HDL levels are known to be inversely related to coronary artery disease (CAD) risk (Gordon et al. 1977; Castelli et al. 1986; Jacobs et al. 1990) this finding is certainly of concern. Noteworthy, an increase in triglyceride levels determined low HDL levels (Deckelbaum et al. 1984; Schaefer et al. 1987) and hypertriglyceridemia itself is also recognized as an independent risk factor in women (Castelli 1986; Castelli 1988; Bass et al. 1993). Together, these data suggest that SLE itself promotes a proatherogenic lipid profile.

These abnormalities observed in untreated active and inactive SLE might be explained by an accumulation of the main triglyceride-rich lipoproteins, namely chylomicrons and VLDL. In their catabolism, both lipoproteins undergo degradation by lipoprotein lipase (LPL) which is the enzyme involved in the lipolysis process (Goldberg 1996). Indeed, a low LPL activity results in accumulation of not only chylomicron but also VLDL, leading to high TG and low HDL levels (Deckelbaum et al. 1984; Schaefer et al. 1987).

Interestingly, a significant impairment of LPL activity in SLE was observed using an *in vitro* lipolysis assay (Borba et al. 2000). Moreover, a striking reduction of the intravascular lipolysis of chylomicron by LPL associated with a pronounced delay in removal of their remnants by liver receptors was also

demonstrated in SLE patients (Borba et al. 2000). Furthermore, the recent description of high frequency of antibodies to lipoprotein lipase (anti-LPL) in SLE raises the possibility that these autoantibodies may modulate LPL activity in SLE (Reichlin et al. 2002; de Carvalho et al. 2004) as has been described for autoimmune hyperlipidemia (Beaumont and Beaumont 1977).

Remarkably, the presence of these autoantibodies was not only significantly associated with increased triglyceride levels (Reichlin et al. 2002; de Carvalho et al. 2004) but also with disease activity (SLEDAI), ESR and CRP (de Carvalho et al. 2004), suggesting that immune mechanism and inflammatory process are concomitantly involved in SLE dyslipoproteinemia.

Cytokines and lupus dyslipoproteinemia

The possible role of inflammation in modulating LPL enzyme is emphasized by the recent description of a significant down-regulation of LPL activity induced by TNF, IL-1 and IFN-gamma (Enholm et al. 1982; Beutler and Cerami 1985; Semb et al. 1987). An enhanced production of these cytokines is a characteristic of SLE, particularly during active disease (Hooks et al. 1982; Tanaka et al. 1988; Maury and Teppo 1989; Spronk et al. 1992).

In this regard, it is known that tumor necrosis factor (TNF) promotes a prompt increase in circulating TG when administered to humans (Feinberg et al. 1988) which is due to an increase hepatic synthesis of VLDL. Moreover, TNF have the ability to inhibit LPL (Beutler et al. 1985). It was recently described that levels of circulating TNF are raised in SLE and correlate with active disease and TG levels (Svenungsson et al. 2003a,b). In addition, TNF activity was closely associated with elevated TGs among SLE patients with previous cardiovascular disease (Svenungsson et al. 2003a). Interestingly, HDL-associated apolipoprotein A-I has been shown to decrease TNF production through its inhibition of contact-mediated activation of monocytes by binding to stimulated T cells (Hyka et al. 2001). In this regard, low HDL levels seem to be not only a consequence of active disease but may also indirectly contribute to enhance inflammation in SLE.

Additionally, in SLE the altered lipid profile may be influenced by high concentrations of two other proatherogenic cytokines: monocyte chemoattractant protein-1 (MCP-1) and IL-6 (Asanuma et al. 2006). In fact, MCP-1 concentrations are related with monocyte infiltration in atherosclerotic lesions and are associated with atherosclerosis in the general population. Moreover, it has been demonstrated that anti-MCP-1 gene therapy limited progression and destabilization of atherosclerosis in animal models (Reckless et al. 1999; Inoue et al. 2002). Interestingly, higher MCP-1 levels were detected in SLE and were

particularly related with disease activity and with increased TG levels (Asanuma et al. 2006). Furthermore, high IL-6 concentrations were associated with low HDL levels (Asanuma et al. 2006) in the same study reinforcing the relevance of cytokines in the lipid profile of SLE patients.

Accordingly, TNF- α and interleukins-1 and 6 are known to stimulate the CRP synthesis by the liver (Gabay and Kushner 1999). The additional observation that these cytokines can affect LPL function (Beutler and Cerami 1985; Semb et al. 1987) further supports their role in lupus dyslipoproteinemia. CRP levels are also increased in the metabolic syndrome (Festa et al. 2000; Tamakoshi et al. 2003; Aronson et al. 2004), hypertriglyceridemia (Grau et al. 1996; Tamakoshi et al. 2003; Fredrikson et al. 2004; Jialal et al. 2004) and in patients with low levels of HDL cholesterol (Tamakoshi et al. 2003; Fredrikson et al. 2004; Jialal et al. 2004).

Other autoantibodies and lupus dyslipoproteinemia

It has been extensively demonstrated that hypertriglyceridemia enhances replacement of cholesterol esters in the core of LDL particles, creating small dense LDL (Richards et al. 1989) which are easily filtered into the arterial wall (Stender and Zilversmit 1981) and more susceptible to oxidation (Chait et al. 1993). Oxidized LDL (oxLDL) may lead to the formation of antigenic neoepitopes that bind to scavenger receptors of macrophages, enhancing oxLDL uptake with subsequent foam cell formation (Heinecke 1997). On the other hand, HDL has an antiatherogenic effect by inhibiting LDL oxidation (Parthasarathy et al. 1990), reducing LDL lipid hydroperoxides (Van Lenten et al. 1995) and oxidized phospholipids (Navab et al. 2004), and transporting oxidized lipids to the liver in the reverse cholesterol transport (Fluiter et al. 1996).

Therefore, the "lupus pattern" of dyslipoproteinemia characterized by hypertriglyceridemia and low HDL should certainly contribute for an enhanced LDL oxidation (oxLDL). Indeed, high levels of oxLDL (i.e. Apo B lipoproteins containing oxPL) were recently identified in this disease (Frostegard et al. 2005). Furthermore, antibodies to oxLDL epitopes were described in SLE (Vaarala et al. 1993; George et al. 1999; Wu et al. 1999; Frostegard et al. 2005). It also seems possible that these antibodies would enhance the accumulation of oxidized LDL to the endothelial wall by increasing LDL uptake via Fc-receptor, as first hypothesized by Vaarala et al. (1993). Of interest, a possible crossreaction between anti-oxLDL and cardiolipin antibodies was also reported in SLE (Vaarala et al. 1993; George et al. 1999; Wu et al. 1999; Frostegard et al. 2005), as well as a cross-reactivity between aCL, anti-HDL and

anti-apoA1 IgG antibodies (Delgado et al. 2003). These findings may explain in part the association of IgG anticardiolipin (aCL) with low HDL and low apolipoprotein A-1 (apoA1) levels in these patients (Lahita et al. 1993). Intriguingly, high levels of anti-apoA1 antibodies were associated to low HDL levels in SLE (Dinu et al. 1998a,b) and further studies are needed to clarify its participation in the HDL metabolism.

High serum levels of oxLDL/ β 2GPI complexes and IgG antibodies to these complexes were also detected in SLE (Kobayashi et al. 2001, 2003; Lopez et al. 2005, 2006). These atherogenic complexes are formed mainly in the atherosclerotic lesions and thus indicate a widespread underlying oxidative injury (Lopez et al. 2006). β 2GPI seems to bind to oxLDL to counteract its inflammatory effect (oxidative) and to promote macrophage uptake via scavenger but the large complexes are usually deposited and promote foam cells formation. In addition, the presence of anti- β 2GPI antibodies enhances *in vitro* macrophage uptake of these complexes (Kobayashi et al. 2001). Interestingly, oxLDL/ β 2GPI complexes and IgG anti- β 2GPI antibodies were detected in lupus patients that had high TG and low HDL levels (Lopez et al. 2006).

Drugs in lupus dyslipoproteinemia

Several drugs commonly used in the treatment of SLE also induce undesirable effects on lipids but corticosteroids are always remembered since their alterations were extensively studied in SLE (Ettinger et al. 1987; Ettinger and Hazzard 1988; Ilowite et al. 1988; MacGregor et al. 1992; Leong et al. 1994; Petri et al. 1994; Bruce et al. 1999).

In fact, chronic corticosteroids use in SLE is associated to increase total plasma cholesterol and its fractions (LDL and HDL) levels, and also TG (Ettinger et al. 1987; Ettinger and Hazzard 1988; Ilowite et al. 1988; MacGregor et al. 1992; Leong et al. 1994; Petri et al. 1994; Bruce et al. 1999), which seem mediated by increased plasma insulin levels and lipid production by the liver, and impaired lipid catabolism (Sholter and Armstrong 2000). This effect could be identified after a short period of 1–2 months of this therapy (Ilowite et al. 1988) and is also dose related since low prednisone daily doses do not significantly alter the lipid profile (MacGregor et al. 1992; Petri et al. 1994). In fact, Petri et al. showed that for each 10 mg increase in prednisone dosage, there is a 7.5 mg% corresponding increase in serum cholesterol and a 1.1 mmHg increase in mean arterial pressure (Petri et al. 1994). In addition, corticosteroids can also indirectly promote other traditional risk factors such as obesity, systemic hypertension, glucose intolerance and diabetes (Petri et al. 1992). Interestingly, Manzi et al. found that corticosteroid use was associated with

myocardial infarct (Manzi et al. 1997) and carotid atherosclerosis in SLE patients, independent of the development or worsening of hypertension and diabetes (Manzi et al. 1999).

On the other hand, a possible antihyperlipidemic property of antimalarials in SLE was first demonstrated in a combined group of patients with rheumatoid arthritis and SLE treated with hydroxychloroquine (Wallace et al. 1990). Subsequently, Petri et al found that the use of hydroxychloroquine was associated with an 8.5% decrease in serum cholesterol (Petri et al. 1994). Thereafter, studies that specifically addressed its effect on lipoproteins in lupus patients had confirmed the beneficial effect on lipids (Hodis et al. 1993; Kavanaugh et al. 1997; Rahman et al. 1999; Borba and Bonfa 2001). Interestingly, a significant increase in HDL levels is observed in SLE patients taking antimalarials with or without prednisone (Borba and Bonfa 2001). Moreover, a beneficial effect in the diabetes control has been suggested in randomized trials after the use of hydroxychloroquine probably by the alteration of insulin resistance (Powrie et al. 1993; Gerstein et al. 2002).

Importantly, several other drugs such as anti-convulsants, antihypertensives (beta blockers and diuretics), estrogen and/or progesterone containing agents should also be considered since they can promote specific alterations on the lipid profile (Henkin et al. 1992).

Associated diseases in lupus dyslipoproteinemia

Renal involvement, such as uremia and nephrotic syndrome, is frequently observed in the course of SLE, and these conditions are known to alter the lipid profile (Appel et al. 1985; Attman and Alaupovic 1991). Also to be considered is the concurrence of other systemic disorders such as thyroid disease and diabetes mellitus, which promote distinct changes in lipoprotein metabolism (Thompson et al. 1981; Brown 1994). Additionally, as patients live longer, lipid abnormalities due to increasing age (Heiss et al. 1980) and menopause (Kannel et al. 1976) may become relevant.

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