Risk Factors in Cardiovascular Disease in Systemic Lupus Erythematosus

Nailú Angélica Sinicato, Priscila Aparecida da Silva Cardoso and Simone Appenzeller*

Department of Medicine, Rheumatology Unit, Faculty of Medical Science, State University of Campinas, Brazil

Abstract: Systemic lupus erythematosus (SLE) is a chronic and multisystemic autoimmune disorder which predominantly affecting women. The most common cause of death in SLE patients affected by disease for more than 5 years is cardiovascular disease (CVD). Epidemiological observations suggest that, together with classical conventional risk factors, other mechanisms (non-conventional/disease-specific factors) promote accelerated atherosclerosis in inflammatory diseases like SLE. Traditional CVD risk factors included age, hypertension, diabetes mellitus, dyslipidemia, previous vascular event defined as previous history of cerebrovascular accidents or ischemic heart disease, menopause and smoking. The non-traditional factors presents in SLE are disease-specific like renal disease manifestation as Lupus nephritis (LN), presence of pro-inflammatory cytokines, some of inflammatory mediators, antiphospholipid antibodies, anti-oxLDL antibodies, corticosteroid uses and cumulative dose of glucocorticoids. We will review traditional and non-traditional risk factors associated with CVD in SLE patients.

Keywords: Nontraditional risk factors, cardiovascular disease, systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic and multisystemic disorder linked to loss of immune tolerance to self-antigens and the production of a variety of autoantibodies predominantly affecting women of childbearing age [1, 2]. 10–20% of all SLE cases occur approximately in the first two decades of life [3]. Its course is characterized by periods of exacerbation and remission with breakthroughs difficulty to be controlled. The most common cause of death in SLE patients affected by disease for more than 5 years is cardiovascular disease (CVD) [4].

Coronary artery disease (CAD) is one of the cardiovascular manifestations observed in young SLE patients. The clinical manifestations of CAD in SLE can result from several pathophysiologic mechanisms, including atherosclerosis, arteritis, thrombosis, embolization, spasm, and abnormal coronary flow [5,6].

The striking clinical characteristic of most patients with SLE who have a myocardial infarction is their young age. This demographic characteristic suggests that patients with SLE are at increased risk of myocardial infarction and that reports of myocardial infarction in patients with SLE do not simply represent chance occurrences. Fatal myocardial infarction has been reported to be 3 times higher in patients with SLE than in age- and gender-matched control subjects [6-8]. Recent case-control series have confirmed that the risk of myocardial infarct in patients with SLE is increased between 9- and 50-fold over that in the general population [6, 7, 9]. It has been increasingly recognized that patients with SLE have a high cardiovascular mortality.

The impact of coronary heart disease (CHD) on morbidity and mortality in patients with established SLE has assumed increasing importance in their long-term management. SLE is a chronic inflammation of organism and inflammation is a prominent feature of atherosclerotic lesions [4]. To prove CVD features in SLE we observed the prevalence of clinically manifest ischemic heart disease has ranged between 8% and 16% in various studies [10-13].

Clinical epidemiological observations strongly suggest that, together with classical conventional risk factors, other mechanisms (non-conventional/disease-specific factors) promote accelerated atherosclerosis in inflammatory diseases like SLE [8,9,14-16]. SLE is now considered to be an independent risk factor for the development of atherosclerosis. Viewing atherosclerosis as an inflammatory disease, this association becomes stronger and better understood.

TRADITIONAL RISK FACTORS

Traditional CVD risk factors included age, hypertension, diabetes mellitus, dyslipidemia, previous vascular event defined as previous history of cerebrovascular accidents or ischemic heart disease, menopause and smoking [17]. Among these factors hypertension, dyslipidemia and hypercholesterolemia have been shown to be more prevalent in SLE [18] (Fig. 1). Metabolic syndrome (MetS) is considered an independent predictor of cardiovascular morbidity and mortality that identifies substantial additional cardiovascular risk beyond the sum of the individual risk factors. In addition to the cardiovascular risk factors that comprise the metabolic syndrome, there is a strong relationship with inflammation [19, 20]. Several studies have shown that the prevalence of MetS is increased in SLE [21-25].
On important finding is that SLE patients have an increased risk for cardiovascular events even after adjustment for Framingham risk factors (hypertension, hypercholesterolemia, diabetes mellitus, older age, and postmenopausal status) [7], so it is necessary to develop other methods to determine the subgroup of SLE patients that are at highest risk for CVD disease. However, traditional CV risk factors alone cannot explain the excess risk of premature CV disease among lupus patients and this suggests that disease-related factors constitute an equal or even greater risk (Fig. 1).

**NON-TRADITIONAL RISK FACTORS**

**Renal Manifestations**

The non-traditional factors present in SLE are Lupus-specific (Fig. 1). Renal disease manifestation like Lupus nephritis (LN) is known to be one of the important factors for accelerated atherosclerosis in SLE [26–29]. Studies had showed that increasing level of serum creatinine and the presence of proteinuria were strongly associated with patients with CVD [30-33]. Elevated serum creatinine and proteinuria indicate renal impairment to a certain extent, which may present as nephritic syndrome. It was reported that nephritic syndrome and excess proteinuria were related to prothrombotic risk, which might lead to the development of clinical CVD [33,34].

**Cytokines**

Pro-inflammatory cytokines released as a result of the chronic systemic inflammation associated with SLE are involved in CVD. Tumoral necrosis factor alpha (TNF-α) which may act in an autocrine manner to modification insulin transduction inhibiting glucose transport, causing in elevated levels, insulin resistance [35]. Studies about TNF-α administration showed that this treatment can causes an increase serum level of triglycerides and very low density lipoproteins in rats and humans [36-38].

SLE patients presents high TNF-α levels, one of the main inhibitors of adipocytokines production; however it was noted that there is an increase in adipocytokine mainly in SLE patients with renal involvement regardless of the TNF-α of the patient [39].

It is known that inflammatory cytokines can stimulate the hypothalamic-pituitary-adrenal (HPA), resulting in an increase in glucocorticoid levels that will affect some immune and inflammatory processes [40,41].

**Inflammatory Mediators**

Some of inflammatory mediators are associated to atherosclerosis, such as: overproduction of c-reactive protein (CRP) a protein that appears in systemic inflammation and can be a strong predictor for CVD [42], fibrinogen, and...
interleukins; IL-10 which has an atheroprotective function, IL-6 one of the most potent proinflammatory cytokines which stimulate the release of fatty acids, and it’s associated with increased cardiovascular mortality and prognosis in the general population [43].

Homocystein is a prothrombotic coagulation factor, that has a toxic effect on endothelium, increases collagen production and decrease nitric oxide availability [9]. Homocysteinemia is considered a new risk factor on atherosclerosis development in SLE patients [9].

**ANTI-PHOSPHOLIPID ANTIBODIES**

Antiphospholipid antibodies are a heterogeneous group of autoantibodies, including, anticyclic lipoprotein antibody (aCL) and lupus anticoagulant (LA), generally directed to phospholipid binding proteins; in this regard, β2GPI represents the major antigenic target [44]. LA has been associated with angina and myocardial infarction [6-47], as well as anti-oxLDL antibodies elevated levels [4,6,31,48,49].

**ANTI-OXIDIZED LOW-DENSITY LIPOPROTEIN (OXLDL)**

During early atherosogenesis, LDL become trapped in the subendothelial space and is subsequently oxidized [50,51]. This oxLDL increases the adhesive properties of endothelial cells and induces the activation of monocytes and T cells and is thought to be responsible for triggering inflammatory responses in macrophages and vascular wall cells [52-54]. This oxLDL is able to take up macrophages and other cells in the atherosclerotic plaque and develop them into foam cells [52]. Anti-oxLDL antibodies are present in patients with atherosclerosis, independently of its etiology [55].

**LUPUS TREATMENT**

As the antiinflammatory/immunosuppressive treatment of patients with SLE continues to improve [56], the contribution of CVD to morbidity and mortality is likely to increase [57].

Corticosteroids has useful factor on reducing disease activity and inflammation, but the cumulative dose of glucocorticoids promote hypertriglyceridemia and insulin resistance and are associated with a higher cholesterol plasma level, higher blood pressure and weight change in lupus patients [58].

Hydroxychloroquine has several protective effect, including effects on the reducing serum lipid profile, increase HDL, reduces the insulin resistance and inhibition of platelet aggregation in SLE [57].

Studies suggests that patients that received early treatment of the disease with pulse IV methylprednisolone to achieve remission, had a lower systolic and diastolic blood pressure, total cholesterol and triglyceride levels proving how it is important in reducing the CV risk among these patients [11,17].

It’s too early to say that mycophenolic acid had an antiatherogenic effect, but recently, studies had examined its potential in view of its multiple roles in inhibiting multiple inflammatory mediators and lymphocytes, particularly T cells and macrophages which play major roles in atherogenesis [17,59].

**CONCLUSION**

In conclusion, in addition to traditional risk factors SLE patients have several disease related risk factors that explain increase CVD. A careful control for this risk factors is essential to continuously improve survival in SLE.

**GRANTS**

Fundação Amparo À Pesquisa Estado São Paulo-Brasil (FAPESP 2008/02917-0 and 2009/06049-6 and 2009/11076-2), Conselho Nacional Pesquisa Desenvolvimento-Brasil CNPq (300447/2009-4)

**DISCLOSURES**

The authors don’t have any conflict of interest; This is an update from a previous version published in this journal Cardiovascular disease in systemic lupus erythematosus: The role of traditional and lupus related risk factors. CCR 2008; 4: 2: 116-122.

**CONFLICT OF INTEREST**

The authors confirm that this article content has no conflicts of interest.

**ACKNOWLEDGEMENTS**

Declared none

**REFERENCES**

[1] Foster MH. T cells and B cells in lupus nephritis. Semin Nephrol 27: 47-58, 2007.
[2] Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006; 15: 308-18.
[3] Merrell M, Shulman LE. Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. J Chronic Dis 1955; 1: 12-32.
[4] Svennungsson E, Jensen-Urdstad K, Heimbürger M, Silveira A, Hamsten A, HamstenU, et al. Risk factors for cardiovascular disease in systemic lupus erythematosus. Circulation 2001; 104: 1887-93.
[5] Haque S, Bruce IN. Therapy insight: systemic lupus erythematosus as a risk factor for cardiovascular disease. Nat Clin Pract Cardiovasc Med 2005; 2: 423-30.
[6] Zeller CB, Appenzeller S. Cardiovascular Disease in Systemic Lupus Erythematosus: The Role of Traditional and Lupus Related Risk Factors, Current Cardiology Reviews, 2008, 4, 116-122
[7] Edsaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001; 44: 23331-7.
[8] Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation 2004; 109: 2-10.
[9] Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med. 1999; 340: 113-26.
[10] Borchers AT, Keen CL, Shoefield Y, Gershwin ME. Surviving the butterfly and the wolf: mortality trends in systemic lupus erythematosus. Autoimmun Rev 2004; 3: 423-53.
[11] Petri M, Perez-Guthmann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992; 93: 513-9.
[12] Gladman DD, Urowitz MB. Morbidity in systemic lupus erythematosus. J Rheumatol 1987; 14: 223-6.

[13] Badui E, Garcia-Rubi D, Robles E, et al. Cardiovascular manifestations in systemic lupus erythematosus. Prospective study of 100 patients. Angiology. 1985; 36: 431-41.

[14] Sattar N, Mccarey DW, Capell H, Mcnnes IB. Explaining how “high-grade” systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003; 108: 2957-63.

[15] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1999; 336: 973-9.

[16] Abou-Raya A, Abou-Raya S. Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmun Rev 2006; 5: 331-7.

[17] Sazliyana S, Shahrir MSM, Norella CTK, et al. Implications of immunosuppressive agents in cardiovascular risks and carotid intima-media thickness among lupus nephritis patients. Lupus 2011; 20: 1260-1266.

[18] Mehta JL, Saldeen TGP, Rand K. Interactive Role of Infection, Inflammation and Traditional Risk Factors in Atherosclerosis and Coronary Artery Disease. JACC 1998; 31: 1217-25.

[19] Chung, C. P., Avalos I., Oeser, A., et al. High prevalence of the metabolic syndrome in patients with systemic lupus erythematosus: association with disease characteristics and cardiovascular risk factors. Ann Rheum Dis 2007; 66: 208-214.

[20] Cheung BM, Ong KL, Man YB, Wong LY, Lau CP, et al. Prevalence of the metabolic syndrome in the United States national health and nutrition examination survey 1999-2002 according to different defining criteria. J Clin Hypertens 2006; 8: 562-70.

[21] Negrom M, Molina MJ, Mayor AM, Rodriguez VE, Vilam L. Factors associated with metabolic syndrome in patients with systemic lupus erythematosus from Puerto Rico. Lupus 2008; 17: 348-54.

[22] Bellomio V, Spindler A, Lacero E, et al. Metabolic Syndrome in Argentinean patients with systemic lupus erythematosus. Lupus 2009; 18: 1019-25.

[23] Mok CC, Poon WL, Lai JPS, et al. Metabolic syndrome, endothe- lial injury, and subclinical atherosclerosis in patients with systemic lupus erythematosus. Scand J Rheumatol 2010; 39: 42-49.

[24] Sabio JM, Zamora-Pasadas M, Jiménez-Jáimez J, et al. Metabolic syndrome in patients with systemic lupus erythematosus from Southern Spain. Lupus 2008; 17: 849-59.

[25] Villar MJ, Azvedo GD, Gadelha RG, et al. Prevalence of metabolic syndrome and its components in Brazilian women with systemic lupus erythematosus: implications for cardiovascular risk. Ann Rheum Dis 2006; 65: 362.

[26] Bulkley BH, Roberts WC. The heart in systemic lupus erythemato- sus and the changes induced in it by corticosteroid therapy. A study of 36 necropsy patients. Am J Med 1975; 58: 243-64.

[27] Serikova S, Kozlovskaiia NL, Shilov EM. [Lupus nephritis as a factor of atherosclerosis risk in patients with systemic lupus erythematosus]. Ter Arkh 2008; 80: 52-8.

[28] Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogrzylo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976; 60: 221-5.

[29] Karsh J, Klippe1 JH, Balow JE, Decker JL. Mortality in lupus nephritis. Arthritis Rheum 1979; 22: 764-9.

[30] Bruce IN, Urowitz MB, Gladman DD, Ibanez D, Steiner G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. Arthritis Rheum 2003; 48: 3159-67.

[31] Doria A, Shoemfeld Y, Wu R, et al. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2003; 62: 1071-7.

[32] Selzer F, Sutton-Tyrell K, Fitzgerald SG, et al. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. Arthritis Rheum 2004; 50: 151-9.

[33] Yang L, Tao J, Tang X et al. Prevalence and correlation of conventional and lupus specific risk factors for cardiovascular disease in Chinese systemic lupus erythematosus patients JEDV 2012; 26: 95-101.

[34] Nickolas TL, Radhakrishnan J, Appel GB. Hyperlipidemia and thrombotic complications in patients with membranous nephropa- thy. Semin Nephrol 2003; 23: 406-11.

[35] Saghizadeh M, Ong JM, Garvey WT, Henry RR, Kern PA: The expression of TNF alpha by human muscle: relationship to insulin resistance. J Clin Invest 1996; 97: 1111-16.

[36] Semb H, Peterson J, Tavener J, Oliveira T, Multiple effects of tumor necrosis factor on lipoprotein lipase in vivo J Biol Chem. 1987; 262: 8390-4.

[37] Grunfeld C, Gulli R, Moser A. H., Gavin L. A., Feingold K. R. Effect of tumor necrosis factor administration in vivo on lipoprotein lipase activity in various tissues of the rat. J Lipid Res 1989; 30: 579-85.

[38] Feingold K, Rod, Suprans I, et al. Effect of tumor necrosis factor (TNF) on lipid metabolism in the diabetic rat. Evidence that inhibition of adipose tissue lipoprotein lipase activity is not required for TNF-induced hyperlipidemia. J Clin Invest 1989; 83: 1116-21.

[39] Ruslan Medzhitov Origin and physiological roles of inflammation. Nature 2008; 454.

[40] Martin-Cordero L, Garcia JJ, Hinchado MD, Ortega E. The interleuken-6 and noradrenaline mediated inflammation-stress feedback mechanism is dysregulated in metabolic syndrome: Effect of exer- cise. Cardiovasc Diabetology 2011; 10: 42.

[41] Besedovsky HO, Del Rey A. Physiology of psychoneuroimmunol- ogy: A personal view. Brain Behav Immun 2007; 21: 34-44.

[42] Sknma C, Ramsby-Goldman R. Management of cardiovascular complications in systemic lupus erythematosus. Int J Clin Rheum- tol. 2010; 5: 75-100.

[43] Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. Am J Med 1999;106:506-12.

[44] Zampieri S, Iacarico L, Ghiardiello A, et al. Systemic lupus erythematosus, atherosclerosis, and autoantibodies. Ann N Y Acad Sci 2005 Jun; 1051: 351-61.

[45] Vaara O, Manttari V, Manninen, et al. Anti-cardioid antibo- dies and risk of myocardial infarction in a prospective cohort of middle-aged men. Circulation 1995; 91: 23-27.

[46] Shery Y, Shemesh J, Tenenbaum A, et al. Coronary calcium and anti-cardioinip antibody are elevated in patients with typical chest pain. Am J Cardiol 2000; 86:1306-1311.

[47] Shery Y, Tenebaum A, Blank M, et al. Coronary artery disease but not coronary calcification is associated with elevated levels of car- diovascular biomarkers: 2-glycoprotein-4, and oxidized-LDL antibodies. Cardiol- ogy 2001; 95: 20-24.

[48] George J, Harats D, Gilburd B, et al. Atherosclerosis-related markers in systemic lupus erythematosus patients: the role of humoral immunity in enhanced atherogenesis. Lupus 1999; 8: 220-226.

[49] Hayem G, Nicaise-Roland P, Palazzo E, et al. Anti-oxidized low- densitylipoprotein (OxLDL) antibodies in systemic lupus erythe- matosus with and without antiphospholipid syndrome. Lupus 2001; 6:351-6.

[50] Nicolio D, Monestier M. Antiphospholipid antibodies and athero- sclerosis. Clin Immunol 2004; 112:183-189.

[51] Shoenfeld Y, Shery Y, George J, Harats D. Autoantibodies associ- ated with atherosclerosis. Ann Med 2000; 32: 37-40.

[52] Frostegard J, Haegestrand A, Gidlund M, Nilsson J. Biologically modified LDL increases the adhesive properties of endothelial cells. Atherosclerosis 1991; 90: 119-126.

[53] Stemme S, Faber B, Holm J, et al. T lymphocytes from human atherosclerotic plaques recognize oxidized low density lipoprotein. Proc Natl Acad Sci USA 1995; 92: 3893-3897.

[54] Frostegård J, Huang YH, Ronnelid J, Schaffer L. Platelet-activating factor and oxidized LDL induce immune activation by a common mechanism. Arterioscler Thromb Vase Biol 1997; 17: 963-968.

[55] Bergmark C, Wu R, de Faire U, Leffvert AK, Swenden J. Pa- tients with early onset of peripheral vascular disease have high levels of autoantibodies against oxidized low-density lipoproteins. Arterioscler Thromb Vase Biol 1995; 15: 441-445.

[56] Urowitz MB, Gladman DD, Abu-Shakra M, Farewell VT. Mortal- ity studies in systemic lupus erythematosus: results from a single
center. III. Improved survival over 24 years. J Rheumatol 1997; 24:1061-5.

[57] Bessant R, Duncan R, Ambler G. et al. Prevalence of Conventional and Lupus-Specific Risk Factors for Cardiovascular Disease in Patients With Systemic Lupus Erythematosus: A Case-Control Study Arthritis & Rheumatism 2006; 55: 892-899

[58] Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003; 349: 2399-2406

[59] van Leuven SI, Kastelein JJ, Allison AC, Hayden MR, Stroes ES. Mycophenolate mofetil (MMF): Firing at the atherosclerotic plaque from different angles? Cardiovasc Res 2006; 69: 341-347.