É A ATEROSCLEROSE UMA DOENÇA INFLAMATÓRIA? / IS ATHEROSCLEROSIS AN INFLAMMATORY DISEASE?

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Cardiovascular disease (CVD) is a major public health problem and the leading cause of death in industrialized nations. In Portugal more than 37 000 deaths per year are attributed to CVD.

It has been recognized that patients with chronic inflammatory diseases, such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) die prematurely largely due to CVD (Goodson NJ *et al.* Arthritis Rheum 2002; 46: 2010-2019; Bruce N Rheumatology 2005; 44:1492-1502). RA patients have a 2-3 times higher risk of myocardial infarction and in young women with SLE, ages 35-44 years, this excess risk is more than 50-fold compared to the general population (Manzi S *et al.* Am J Epidemiol 1997; 145: 408--415). Traditional cardiovascular risk (CV) factors do not explain this increase and Framingham 10 year risk equation underestimates the true cardiovascular risk in this population (Esdaile JM *et al.* Arthrithis Reum 2001; 41:2331-2337).

Atherosclerosis is the main determinant of CV morbidity and mortality. Traditional risk factors such as hypercholesterolemia, hypertension, diabetes, smoking and family history have long been identified as major contributors to the pathogenicity of atherosclerotic lesions. However these risk factors are present in only about 50% of patients with CV events. (Braunwald E. N Eng J Med 1997; 337: 1360-1369). Therefore, other determinants for atherosclerosis and CV events remain to be identified.

Atherosclerosis is now accepted to be a multifactorial process where inflammation plays a crucial role at each stage of the pathology. Disrupted endothelial homeostasis and infiltration of the intima by activated T cells (CD4+, HLA-DR+ and IL-2R+) and monocytes are observed in earlier stages. Local production of a variety of inflammatory mediators including interleukin (IL)-1, tumor necrosis factor-alpha (TNF-alpha), lymphotoxin alpha (LTA), IL-2, IL-6, IL-8 and interferon gamma, which can modulate and perpetuate the immunologic reaction within atherosclerotic lesions, have been demonstrated. Ongoing inflammation stimulates smooth muscle cell proli-

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feration, artery wall remodelling and foam-cell formation (i.e. fatty--streaks). Further injury includes focal necrosis and a fibroproliferative healing process that narrows the vessel lumen and alters blood flow (i.e. atherosclerotic plaque). Calcification is a frequent finding in advanced atherosclerosis. Plaque disruption and subsequent thrombosis is the major cause of symptoms and clinical events (Russel R. N Eng J Med 1999; 340: 115-126). A state of chronic inflammation of the arterial wall may contribute to haemorheological disturbances. The adhesive interactions between white blood cells and the endothelium may be affected by the erythrocyte aggregation tendency. Temporary occlusion could occur also as a result of local oedema and swelling of the tissue producing local hemoconcentration and increased blood viscosity.There is evidence from longitudinal as well from follow-up studies that haemorheologic profile is accompanied by similar variations in the inflammatory profile (Luquita A *et al.* Clin Hemorheol Microcirc). Hence it is expected that patients with SLE and RA might have abnormal values of haemorheological parameters namely increased whole blood viscosity, plasma viscosity and aggregation, and decreased erythrocyte deformability that are characteristics of inflammatory states.

Additionally, chronic inflammatory mediators are believed to contribute to the atherosclerotic process, yet the interaction between these mediators on specific atherogenic processes remains to be elucidated. Increased levels of C-reactive protein (CRP), IL-6, TNF superfamily cytokines, and adhesion molecules independently predict the risk of future CV events in the general population (Danesh J. N Eng J Med 2004; 350: 1387-1397; Reilly MP J Investig Med. 2007; 55: 26-35). On the other hand, chronic inflammation may aggravate traditional CV risk, inducing a more proatherogenic lipid pattern and decreasing insulin sensitivity (Dessein PH *et al.* Arthritis Res. 2002; 4: R5).

TNF-alpha is one of the best--studied proinflammatory cytokines, crucial in RA pathophysiology, which has emerged as an important contributor to the development of atherosclerotic lesions. It acts by promoting the expression of adhesion molecules on endothelial cells and the recruitment and activation of inflammatory cells and initiates an inflammatory cascade within the arterial wall. In addition, TNF-alpha induces insulin resistance and modifies plasma lipids, suggesting that the increase in the production of this cytokine is an early and central event in atherogenesis (Skoog T *et al.* Eur Heart J 2002; 23: 376-383; Hotamisligil GS et al. Science 1993; 259: 87-91). In fact, TNF alpha increases triglyceride level, decreases HDL and total cholesterol and is likely to induce changes in LDL composition that eventually increase the atherogenicity of this particle. Reinforcing this, blockade of TNF-alpha in RA patients has a positive effect on insulin resistance, lipid profile at short term and risk of developing CV events (Gonzalez-Gay MA *et al.* Clin Exp Rheumatol. 2006; 24: 83-86; Popa C *et al.* Ann Rheum Dis. 2007 66:1503--1507; Jacobsson LT *et al.* J Rheumatol 2005; 32:1213-1218).

Lymphotoxin-alpha (LTA) is also a proinflammatory cytokine structu-

rally similar to TNF-alpha. The role of LTA in atherosclerosis is poorly characterized, but in rodents it seems more relevant in promoting atherosclerotic lesions than TNF-alpha. In LTA knockout mice there is a three fold reduction in atherosclerotic lesion size, lower levels of total cholesterol and higher levels of HDL, as compared to the TNF-alpha deficient mice (Scheryer S *et al.* J Biol Chem 2002; 277: 12364-12368).

More recently a link between bone remodelling cytokines, in particular osteoprotegerin (OPG), and atheroma calcification was identified. Local atheroma and circulating levels of this cytokine have been associated with CV events in a variety of patient populations, but its exact role remains controversial (Kiechl S *et al* Circulation 2004; 109:2175-2180).

Vitamin D may represent another link between bone metabolism and CVD. Beyond its effect on mineral metabolism, vitamin D exhibits anti-inflammatory and antiproliferative effects and may protect against CV mortality (Levin A *et al.* Kidney Int 2005; 68:1973-1981). Interestingly, as we have stated before, RA and SLE seriously disrupt bone metabolism and influence the RANKL/OPG system (Fonseca JE *et al.* Clin Exp Rheumatol 2005; 23: 185-92).

Moreover, several lines of evidence suggest that genetic traits contribute to the risk of CVD, but the precise magnitude of its influence is poorly described. Genetic factors may interact with the environment and modulate atherosclerosis-related process, including inflammation. Polymorphisms in the -308 TNF promoter position predispose to the development of coronary artery disease (Sbarsi I *et al.* Int J Immunopathol Pharmacol 2007; 20:145-154) and as confirmed in our patients are also associated with a worse outcome and with the response pattern to treatment in RA (Fonseca JE *et al.* Ann Rheum Dis 2005; 64: 793-794; Fonseca JE et al Arthritis Res Ther 2007; 9: R37;). Polymorphisms of the LTA gene have been associated with increased levels of CRP, carotid artery atherosclerosis, myocardial and cerebral infarction (Naoum JJ *et al.* Med Sci Monit 2006; 12:RA121-124). This was not confirmed in a multinational trial, but the heterogeneity of the population genetic background limits the interpretation of the results.