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Subclinical Atherosclerosis in Systemic Autoimmune Disorders

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1. Introduction

Over the last years, accelerated atherosclerosis with consequent increased prevalence of cardiovascular disease (CV) in autoimmune patients, especially rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) has been well established (Toloza, Uribe et al. 2004). However, traditional risk factors associated with atherosclerosis including among others smoking, dyslipidemia, diabetes mellitus (DM), hypertension (HT) and increased body mass index (BMI), do not fully account for the high rates of subclinical atherosclerosis in these patients (Meune, Touze et al. 2009). In the present review, traditional and disease related risk factors of CV disease in the setting of chronic autoimmune disorders with special focus in RA, SLE and Sjogren's syndrome (SS) will be discussed.

2. Epidemiology of CV disease in systemic autoimmune disorders

RA

RA, a chronic systemic inflammatory disease affecting 0.5–1% of the adult population is associated with a two fold increase of CV disease. In a recent study by Evans et al, in 636 RA patients, the incidence of acute coronary syndromes (ACS) including myocardial infarction, unstable angina, cardiac arrest or death due to ischemic heart disease was 3.5 per 100 patient-years with the presence of carotid plaque, CV risk factors (particularly diabetes or hypertension), active polyarticular disease, high cumulative dose of glucocorticoids and male sex, being high risk contributors (Evans, Escalante et al. 2011). In patients with early RA, higher intima media thickness (IMT) scores- a surrogate marker of subclinical atherosclerosis- have been detected compared to healthy controls (Sodergren, Karp et al. 2010) (Georgiadis, Voulgari et al. 2008). Of interest, treatment with methotrexate and prednisolone led to significant reduction of IMT scores compared to baseline after one year of treatment. Several studies so far have demonstrated the independent relationship of elevated inflammatory markers (Myasoedova and Gabriel 2010), with the effects of the atherosclerotic process being reversed, after disease activity and chronic inflammation in RA patients are controlled (Bisoendial, Stroes et al. 2011).

SLE

SLE is a highly heterogeneous autoimmune disease, affecting women of childbearing age, with substantial mortality and morbidity. The effect of SLE on atherosclerotic disease has been recognised since the 70s, when Urowitz et al displayed a bimodal mortality peak; the first was attributed to disease activity and infections and the second to CV disease (Urowitz, Bookman et al. 1976). The prevalence of ischemic heart disease in SLE patients is estimated between 8% and 16% (Badui, Garcia-Rubi et al. 1985; Gladman and Urowitz 1987; Petri, Perez-Gutthann et al. 1992; Borchers, Keen et al. 2004) conferring a 50fold risk (Manzi, Meilahn et al. 1997). In regard to subclinical coronary artery disease, the rates seem to be even higher, reaching the percentage of 28%-40% (Manzi, Selzer et al. 1999; Svenungsson, Jensen-Urstad et al. 2001; Asanuma, Oeser et al. 2003; Manger, Kusus et al. 2003; Roman, Shanker et al. 2003; Vlachoyiannopoulos, Kanellopoulos et al. 2003). Esdaile et al revealed that even after statistical correction for the effects of all classical CV risk factors, patients with SLE still had a 7.9-fold increase in the risk of stroke and a 10.1-fold increase in risk of non-fatal myocardial infarction (Esdaile, Abrahamowicz et al. 2001). Given that standard Framingham scores cannot fully account for the rate of ischemic events, lupus is now regarded as an independent risk factor for the development of CV comorbidity (Manzi, Meilahn et al. 1997; Manzi 2000).

SS

SS or autoimmune epithelitis a slowly progressive autoimmune disease is characterized by salivary and lacrimal gland dysfunction and shares many common clinical and serologic features with other immune mediated autoimmune diseases especially SLE (Mavragani and Moutsopoulos 2010). SS has been recently associated with increased rates of subclinical CV disease in a limited number of studies. Vaudo et al, revealed higher carotid and femoral IMT scores in 37 untreated white women with primary SS compared to age and sex matched healthy counterparts, in association with leukopenia and the presence of anti-SSA antibodies (Vaudo, Bocci et al. 2005). In a subsequent study by Satish et al, patients with long standing disease demonstrated abnormal ankle brachial index (ABI) values compared to controls (Rachapalli, Kiely et al. 2009). While endothelium dependent flow mediated vasodilation (FMD) –a marker of endothelial function- did not differ significantly between primary SS patients and controls as a whole, the subset of patients with articular involvement or parotid gland enlargement had lower values of FMV than controls and patients without such characteristics.

On the other hand, nitrate mediated vasodilation (NMV) values -detecting smooth muscle relaxation independently of endothelial contribution- were lower in primary SS patients and particularly in those characterized by leukopenia, rheumatoid factor (RF), anti-SSB antibodies, and articular involvement. Of interest, NMV values, were directly correlated to the number of the circulating white blood cells and inversely correlated to vascular cell adhesion molecule 1 (VCAM-1) levels (Gerli, Vaudo et al. 2010).

3. Traditional CV risk factors in autoimmune diseases

3.1 Metabolic syndrome

The metabolic syndrome (MetS) describes a constellation of major risk factors for CV disease including dyslipidemia, obesity, hypertension and insulin resistance. Several studies so far

have documented the increased frequency of MetS in patients with chronic rheumatic diseases compared to healthy control populations; the higher proinflammatory cytokine burden impairs insulin sensitivity and promotes the adverse lipoprotein profile seen in MetS (Pereira, de Carvalho et al. 2009; Santos and Fonseca 2009).

RA

The relationship between the BMI and overall CV mortality in patients with RA is well recognised (Kitas and Gabriel 2011). Quite unexpectedly, compared to the general population, the risk of CV disease in RA patients is increased in younger females with low body mass index ($<20\text{kg/m}^2$), most likely due to the excess of inflammatory cytokines (Gabriel 2010; Ozbalkan, Efe et al. 2010; Kitas and Gabriel 2011). In accord with the previous observation, obesity is linked to hypertension and dyslipidemia, but with lower RA disease activity and consequently less CV mortality (Summers, Metsios et al. 2010). In contrast, in the study of Kallinoglou et al, multivariate analysis revealed an association of obesity with CV disease in patients with RA mainly due to concomitant presence of risk factors such as HT, high-density lipoprotein (HDL), insulin resistance and Mets (Stavropoulos-Kalinoglou, Metsios et al. 2009). On the other hand, a recent study has shown that in patients with established RA, both very low and very high BMI and BF associate independently with increased disease activity and physical dysfunction but not with the presence of erosions or joint surgery (Stavropoulos-Kalinoglou, Metsios et al. 2009). While the long-term use of glucocorticoids in RA may collectively contribute to the development of Mets syndrome and atherosclerosis, no association with long term low dose glucocorticoid has been detected in this population (Toms, Panoulas et al. 2008). Furthermore, Ku et al showed that RA patients have high basal levels of insulin and increased insulin resistance and that the degree of severity correlates with inflammatory indices (Ku, Imboden et al. 2009). Finally, in a study of a group of 105 Vietnamese women with early RA, a higher prevalence of MetS compared with healthy controls was demonstrated with disease activity, high inflammatory indices, disability score and less use of DMARDs being independent predictors (Dao, Do et al. 2010). The link between obesity and inflammation has recently attracted particular attention. Adipocytokines –a newly identified cytokine subset- have been associated with adipose tissue and include among others leptin, adiponectin, resistin and visfatin. Leptin is essential for the regulation of appetite and body weight, as well as the modulation of immune responses (Rho, Chung et al. 2010). While resistin and visfatin are associated with inflammation, insulin resistance and subclinical atherosclerosis, adiponectin is mainly anti-inflammatory, and inversely associated with obesity, insulin resistance, CRP and CV risk (Fagerer and Kullich 2010; Yoshino, Kusunoki et al. 2011).

In patients with RA, higher levels of adipocytokines have been detected compared to control subjects. In a recent report, leptin and visfatin levels were associated with insulin resistance, but not with the presence of coronary calcification (Ozgen, Koca et al. 2010; Rho, Chung et al. 2010). As expected, in contrast to adiponectin, which was negatively associated with CRP, leptin and resistin levels were positively linked to CRP titers (Yoshino, Kusunoki et al. 2011).

While anti-tumor necrosis factor alpha (anti-TNF) treatment in RA patients does not change the levels of circulating visfatin and leptin (Popa, Netea et al. 2009; Gonzalez-Gay, Vazquez-Rodriguez et al. 2010), data on adiponectin is contradictory. In the largest so far study including 97 patients with RA, serum adiponectin was increased after 12 months of anti-TNF treatment (Nishida, Okada et al. 2008), an observation also confirmed in smaller reports with the same follow-up period, implying a potential underlying mechanism for CV

risk reduction by anti-TNF agents (Komai, Morita et al. 2007; Serelis, Kontogianni et al. 2008; Engvall, Tengstrand et al. 2010). In contrast, with the exception of the Japanese study by Komai et al who revealed increased adiponectin levels as soon as 2 and 6 weeks, no changes or reduction in adiponectin levels have been reported by studies with a follow-up period of 6 months (Derdemezis, Filippatos et al. 2009; Popa, Netea et al. 2009).

SLE

In a large cohort of 250 patients with SLE and equal number of age-sex matched controls, increased waist-to-hip ratio and sedentary lifestyle in SLE patients was found (Bruce, Urowitz et al. 2003). The prevalence of obesity in SLE has been recently estimated in a cohort of 145 patients by two methods. Using the most common body composition measure (Body mass index, BMI), almost 30% were obese; using a more sensitive measure (by Dual X-ray absorptometry (DXA), the percentage rose to 50% (Katz, Gregorich et al. 2011). A higher prevalence of Mets was found in young lupus patients below 40 years compared to age matched controls (15.8% vs 4.2%) (Sabio, Zamora-Pasadas et al. 2008); the corresponding figures in the study of Chung et al were 32.4% versus 10.9% (using the WHO definition that requires direct determination of insulin resistance) and 29.4% versus 19.8% (using the National Cholesterol Education Program Adult Treatment Panel III definition -NCEP) and found to correlate with higher C-Reactive protein (CRP) levels and endothelial injury. In a subsequent study by Mok et al, the prevalence of Mets was 16.3% in lupus patients and correlated with coronary atherosclerosis (Mok, Poon et al. 2010). In another report, the presence of Mets was associated with higher aortic pulse wave velocity (PWV) –as an indicator of arterial stiffness- and increased biomarkers of subclinical atherosclerosis such as CRP, IL-6, C3, uric acid, homocysteine, fibrinogen and D-dimer (Sabio, Vargas-Hitos et al. 2009). Insulin resistance per se as defined by the WHO criteria was more prevalent in lupus patients compared to controls (44.1% versus 24.8%) (Chung, Avalos et al. 2007).

Similarly to RA, increased levels of adiponectin have been reported in SLE patients (Sada, Yamasaki et al. 2006; Chung, Long et al. 2009; Vadacca, Margiotta et al. 2009) and found to be associated with carotid plaque formation, as a physiologic attempt to limit endothelial damage (Sada, Yamasaki et al. 2006; Vadacca, Margiotta et al. 2009; Clancy and Ginzler 2010; Reynolds, Buyon et al. 2010). Opposite are the findings reported by Chung et al, where lower levels of adiponectin were associated with insulin resistance, BMI and CRP but not with coronary atherosclerosis (Chung, Long et al. 2009). In a murine lupus model, adiponectin has been recently shown to exert protective effects against lupus activity and concomitant atherosclerotic disease. The use of the peroxisome proliferator-activated receptor gamma (PPARgamma) agonist rosiglitazone reduces autoantibody production, renal disease, and atherosclerosis in mouse models of SLE possibly through adiponectin induction. At the same time, lupus mice that lack adiponectin develop more severe disease compared to adiponectin-sufficient lupus mice with the administration of exogenous adiponectin ameliorating disease (Aprahamian, Bonegio et al. 2009). Leptin levels were associated with insulin resistance, BMI and CRP but not with coronary or carotid atherosclerosis (Vadacca, Margiotta et al. 2009). Administration of leptin in lupus prone model led to increased pro-inflammatory HDL scores, atherosclerosis, and accelerated proteinuria, revealing its proatherogenic role (Hahn, Lourencco et al. 2010).

SS

In patients with SS, a higher prevalence of associated dyslipidemia, DM, and hyperuricemia compared to age and sex-matched controls has been observed. Hypercholesterolemia was

associated with a lower frequency of immunological markers such as anti-Ro/SSA, anti-La/SSB antibodies, low C3, and C4 levels, while hypertriglyceridemia and DM were positively associated with the presence of extraglandular (renal, liver, vasculitic) involvement. A higher prevalence of DM was found in patients treated with corticosteroids (Ramos-Casals, Brito-Zeron et al. 2007).

3.2 Hypertension (HT)

RA

The prevalence of HT among patients with RA varies between different studies (Panoulas, Metsios et al. 2008). In the largest so far population study by Han et al. prevalence of HT was significantly higher in RA (34% vs 23.4%). However, a recent metaanalysis assessing the effect of traditional risk factors in the pathogenesis of CV disease in RA patients demonstrated similar rates of hypertension in RA patients compared to healthy controls (Gabriel 2010; Boyer, Gourraud et al. 2011).

HT has been found to be associated with subclinical atherosclerosis and CV morbidity in RA patients (Panoulas, Douglas et al. 2007). In a recent Greek cohort study of 325 RA patients, with late disease onset, inadequate early control of disease activity and leflunomide treatment, hypertension was clearly demonstrated to be an important risk factor for CV disease (Serelis, Panagiotakos et al. 2011).

HT and low grade inflammation have been previously linked in general population studies (Panoulas, Douglas et al. 2007; Kitas and Gabriel 2011). High CRP leads to vasoconstriction through reduction of endothelial nitric oxide production, increase in expression of endothelin-1 and upregulation of angiotensin type 1 receptor expression; furthermore, it induces platelet adherence, oxidation and thrombosis. Apart from systemic inflammation, physical inactivity due to articular involvement, genetic predisposition, various medications including NSAIDs, corticosteroids, leflunomide and cyclosporine might account for deregulated arterial pressure in patients with RA (Stavropoulos-Kalinoglou, Metsios et al. 2009; Kitas and Gabriel 2011).

Genetic contribution in occurrence of HT in RA patients was evidenced by the association of previously associated polymorphisms with HT in healthy populations. In RA patients, TGFB1 869T/C and endothelin gene polymorphisms have been shown to be linked with HT, with the latter found to be associated with raised endothelin-1 (ET-1) levels. In contrast to previous studies in healthy subjects, no associations between IL-6-174G/C and HT (Panoulas, Douglas et al. 2009) was detected. Furthermore, a cross-sectional study did not demonstrate significant associations between RA disease activity and hypertension (Panoulas, Metsios et al. 2008; Kitas and Gabriel 2011).

SLE

HT is a well recognised risk factor for CV disease development in SLE patients (Petri, Perez-Gutthann et al. 1992) as evidenced by several studies reporting its contribution in plaque formation (IMT measurement, coronary angiography) and arterial stiffening (Sella, Sato et al. 2003; Selzer, Sutton-Tyrrell et al. 2004; Maksimowicz-McKinnon, Magder et al. 2006; Cypiene, Dadoniene et al. 2010; Gallelli, Burdick et al. 2010). Several studies so far have confirmed the increased prevalence of arterial HT in these patients, ranging from 33% to 56% (de Leeuw, Freire et al. 2006; Bellomio, Spindler et al. 2009; Duarte, Couto et al. 2009; Boucelma, Haddoum et al. 2011; Sabio, Vargas-Hitos et al. 2011). In an effort to investigate

the contributors of HT in a cohort of 112 lupus patients, Sabio et al, reported that renal disease, insulin levels and disease activity indices such as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) were independent predictors of HT in these subjects. Of interest, in the younger age group (<40y), hypertension was also associated with higher non obesity-related insulin levels, while in the older group (>40y), with age and obesity (Sabio, Vargas-Hitos et al. 2011).

Arterial hypertension did not seem to influence subclinical atherosclerotic disease in patients with pSS (Vaudo, Bocci et al. 2005; Rachapalli, Kiely et al. 2009; Gerli, Vaudo et al. 2010).

3.3 Dyslipidemia

Increased levels of total cholesterol (TC), low-density-lipoprotein (LDL) cholesterol and decreased level of HDL cholesterol are associated with increased risk for CV disease in the general population (Nurmohamed 2009). Cholesterol is transported in the blood by LDL which contains esterified cholesterol and triglycerides surrounded by phospholipids, free cholesterol and apolipoprotein B100 (ApoB100). Circulating LDL particles can accumulate in the intima, where ApoB100 binds to proteoglycans of the extracellular matrix, they are oxidised (Hansson and Hermansson 2011) (oxLDLs), become proinflammatory and lead to endothelial activation. Monocytes are stimulated by macrophage colony-stimulating factor produced by activated endothelial cells and differentiate into macrophages. Macrophages upregulate their scavenger receptors that can take up oxLDL (Hahn, Grossman et al. 2008). Cholesterol accumulation in macrophages transforms them into foam cells that are characteristic of the atherosclerotic lesion. Dendritic cells (DCs) may take up LDL for antigen presentation in regional lymph nodes. In the normal artery wall, DCs promote antigen tolerization; however, atherogenesis leads to a switch from tolerance to the activation of adaptive immunity (Hansson and Hermansson 2011). Monocytes attract lymphocytes that recognize antigens and contribute to inflammation by releasing cytokines. As plaque matures, proteases and other proinflammatory molecules are produced, with hypertrophy of smooth muscle, damage to endothelial cells, bulging of plaque into the lumen of the artery, and formation of a fibrous cap over the plaque (Hahn, Grossman et al. 2008).

RA

Lipoprotein (α) (Lp(α)) is a cholesterol-rich modified form of LDL (Van Doornum, McColl et al. 2002) that is transformed in the liver by covalent attachment of ApoB to ApoA, a member of the plasminogen gene family (Tabas, Williams et al. 2007). Lp(α) has been identified as an independent risk factor for coronary heart disease and elevated levels have been demonstrated in RA patients with active disease (Van Doornum, McColl et al. 2002). Several studies suggest that Lp(α) is associated with early atherosclerosis in RA and possibly in other autoimmune disorders (Dursunoglu, Evrengul et al. 2005; Wang, Hu et al. 2008). In recent studies, complexes of β2-glycoprotein I with Lp(α) ((β2)-GPI-Lp(α)) are found in sera of active RA patients and associate with oxLDL, ox-Lpa and CRP levels (Zhang, Li et al. 2011).

On the other hand, low HDL levels have been previously associated with RA related atherosclerosis implying the potential link between HDL and autoimmunity. HDL possesses anti-inflammatory effects and inhibits the ability of antigen-presenting cells (APCs) to stimulate T cells (Yu, Wang et al. 2010). Given that inflammation has been shown to

suppress total and LDL cholesterol, active RA patients have lower total cholesterol, low LDL and depressed HDL resulting in a higher atherogenic index (total cholesterol/HDL-cholesterol ratio) (Nurmohamed 2009; Kitas and Gabriel 2011), although such alterations have been also observed 3-5 year prior to RA incidence (Myasoedova, Crowson et al. 2010). In a study of early RA patients higher levels of TC, LDL, triglycerides and very low levels in HDL have been observed compared to healthy controls resulting again in a significantly higher atherogenic ratio of TC/HDL as well as that of LDL/HDL (Georgiadis, Papavasiliou et al. 2006). Raised autoantibody titers against oxLDL and low lipoprotein-associated phospholipase A2 (Lp-PLA2) plasma activity have been also suggested as potential contributors in the pathogenesis of accelerated atherosclerosis in patients with early RA (Lourida, Georgiadis et al. 2007). Of interest, recent findings have revealed the contribution of several known RA susceptible genes such as TRAF1/C5, STAT4 and HLA-DRB1-SE in dyslipidemia observed in these patients (Toms, Panoulas et al. 2011).

Systemic inflammation, drug therapy, lifestyle and genetic factors can result not only in changes of overall lipid levels, but also can modify lipids structure and function (Toms, Symmons et al. 2010). Paraoxonase 1 (PON1) is an antiatherogenic enzyme with the ability to destroy biologically active oxLDL (Hahn, Grossman et al. 2008) and to protect LDL against oxidation (Zhao 2009). PON1 activity in RA patients is inversely related to CRP levels, suggesting that inflammation modulates PON activity (Ku, Imboden et al. 2009).

SLE

The classical pattern of dyslipoproteinemia in SLE is characterized by elevated levels of very-low-density lipoprotein cholesterol (VLDL), triglycerides and LDL and low levels of HDL (Borba, Bonfa et al. 2000), although HDL qualitative abnormalities such as peroxidation have been also described, often in association with active disease. Peroxidised HDLs (piHDLs) are unable to reverse cholesterol transport which normally clears oxLDL from the subendothelial space promoting endothelial injury. piHDLs occur in a larger proportion of patients with SLE compared to RA and are associated with carotid artery plaque formation, documented CV disease and low physical activity (McMahon, Grossman et al. 2006; McMahon, Grossman et al. 2009; Volkmann, Grossman et al. 2010).

Apart from HDL, LDL can be also modified in SLE; Frostergard et al disclosed higher levels of oxidized epitopes on LDL in lupus patients compared to controls, which were associated with arterial disease and renal manifestations (Frostergard, Svenungsson et al. 2005).

In a recent study, circulating lipoprotein remnant particles and the intermediate density lipoprotein (IDL) fraction have been strongly associated with IMT values in lupus patients (Gonzalez, Ribalta et al. 2010). Furthermore, reduced levels of apoA-I -the major apolipoprotein component of HDL- have been found in SLE patients with IgG anticardiolipin antibodies (Delgado Alves, Kumar et al. 2003) while antibodies to apoA-I have been previously documented in 32.5% of patients with SLE and 22.9% of patients with primary antiphospholipid syndrome (Dinu, Merrill et al. 1998).

Anti-HDL, anti-CRP anti-Apo A-I have been detected in SLE patients, with the latter found to be associated with persistent disease activity. In the subset of patients with lupus nephritis, anti-Apo A-I and anti-HDL levels correlated with serum anti-double-stranded DNA levels (O'Neill, Giles et al. 2010). Woo et al evaluated the effects of L-4F, (apolipoprotein A-1 mimetic peptide), alone or with pravastatin, in apoE-/-Fas-/-C57BL/6 female mice that spontaneously develop immunoglobulin G (IgG) autoantibodies, glomerulonephritis, osteopenia, and atherosclerotic lesions. As expected, L-4F treatment,

significantly reduced IgG anti-dsDNA and IgG anti-oxPLs (anti-oxidised phospholipids), proteinuria, glomerulonephritis, and osteopenia in a murine lupus model of accelerated atherosclerosis (Woo, Lin et al. 2010).

SS

Low HDL cholesterol levels was a constant finding among SS patients in several studies (Vaudo, Bocci et al. 2005; Lodde, Sankar et al. 2006; Gerli, Vaudo et al. 2010). Of interest, HDL along with total cholesterol were found to be associated with immunoglobulin G levels. In particular, the presence of anti-SSA and anti-SSB antibodies have been linked to lower total cholesterol and reduced HDL cholesterol levels, respectively (Lodde, Sankar et al. 2006). Subsequently, Cruz et al, showed a trend to dyslipidemia defined as total cholesterol >200mg/dL, HDL cholesterol<40mg/dL, LDL cholesterol>130mg/dL or triglycerides > 150mg/dL in patients with pSS compared to controls (Cruz, Fialho et al. 2010).

3.4 Smoking

RA

Smoking is an important risk factor for the development of both RA and CVD. Smoking is associated with severe RA with more erosive disease and extra-articular involvement, as smokers are more likely to have positive RF and anti-CCP antibodies. It is not yet clear if smoking confers the same relative risk for CVD development in RA patients compared to the general population (Ozbalkan, Efe et al. 2010). Cigarette smoking is associated with reduced BMI and body fat (BF) in patients with RA, with heavy smoking particularly linked to lower muscle mass while smoking cessation appears to associate with increased BMI, BF, and waist circumference in these patients (Stavropoulos-Kalinoglou, Metsios et al. 2008). In a recent metaanalysis by Gabriel, the prevalence of smoking, but not of the other traditional CV risk factors appears to be increased in RA compared to non-RA patients, at the time of RA incidence (Gabriel 2010).

SLE

Cigarette smoking along with HT have been identified as the main predictors of extracranial carotid artery atherosclerosis, in an early study including 240 SLE patients (Homer, Ingall et al. 1991). While in the studies conducted by Asanuma and Roman, no association between smoking and carotid or coronary atherosclerosis was detected (Asanuma, Oeser et al. 2003; Roman, Shanker et al. 2003), in a subsequent multiethnic US cohort of 546 SLE patients, the role of smoking in the development of vascular events (cardiovascular, cerebrovascular and peripheral) has been suggested (Toloza, Uribe et al. 2004). Similarly, Selzer et al, compared risk factors for subclinical vascular disease in different vascular beds (carotid and aorta) in SLE female patients. Smoking was identified as a factor correlating with carotid plaque severity, together with older age, systolic hypertension and lower albumin levels. In regard to aortic stiffness, risk factors included older age and higher systolic blood pressure but not smoking (Selzer, Sutton-Tyrrell et al. 2004). Finally, a race-smoking interaction was also identified, as amongst black women with SLE, those with a history of smoking have higher IMT values than non smokers. This effect did not apply to white patients (Scalzi, Bhatt et al. 2009).

Smoking did not seem to influence subclinical atherosclerotic disease in patients with pSS (Vaudo, Bocci et al. 2005; Gerli, Vaudo et al. 2010).

3.5 Hyperhomocysteinemia

Hyperhomocysteinemia is a recognised risk factor for arterial and venous disease in the general population. Homocysteine increases oxidative stress on the endothelium and causes modification of LDL, inhibition of nitric oxide synthesis, proliferation of smooth muscle cells, intimal hyperplasia, increased protease activity, activation of proinflammatory mediators and thrombosis (Durga, Verhoef et al. 2004). Hyperhomocysteinemia can originate either from a genetic polymorphism and/or a variety of factors including folic acid or vitamin B12 deficiency, corticosteroid or methotrexate treatment, and renal dysfunction. Hyperhomocysteinemia has been reported in 20%-42% of patients with RA and is related to treatment with antifolate agents and greater disease activity. Genetic investigations identified the C677T polymorphism in the gene coding for the MTHFR enzyme as a new candidate genetic risk factor for CV disease in the general population. The 677TT genotype is associated with higher plasma homocysteine levels than in heterozygotes or in individuals with wild-type C alleles (Palomino-Morales, Gonzalez-Juanatey et al. 2010). The increased levels of homocysteine caused by methotrexate therapy occur more often to patients heterozygous for the C677T mutation. Normal homocysteine levels are restored by folic acid supplementation (El Bouchti, Sordet et al. 2008).

RA

In a recent Spanish study of RA patients, the MTHFR A1298C rather the C677T was associated with increased risk of atherosclerosis, demonstrating that patients homozygous for the MTHFR 1298CC genotype had increased risk of CV events at 5 and 10 years follow up and more severe endothelial dysfunction (lower values of FMD %), when compared with those homozygous for the wild MTHFR 1298AA genotype (Palomino-Morales, Gonzalez-Juanatey et al. 2010). Interestingly an ongoing study from our group indicate that Greek RA patients with carotid or femoral plaque formation have a higher prevalence of MTHFR AC and CC genotypes compared with those without. The so far available results show that MTHFR 1298 A>C gene polymorphism confers an increased risk for plaque formation (Mavragani 2011).

SLE

Attention has been drawn over the past few years to the role of homocysteine concentration in the development of subclinical atherosclerosis in SLE patients. In a prospective study, Petri identified elevated homocysteine levels as a risk factor for the later development of CV disease in SLE patients (Petri 2000).

In the Toronto Risk Factor Study for coronary heart disease, SLE patients had homocysteine values >15 μmoles/liter in a larger proportion compared to controls (11.6% versus 0.8%) despite having higher folate blood levels (Bruce, Urowitz et al. 2003). SLE patients with hyperhomocysteinemia have a threefold increase in odds ratio of thrombotic event (Refai, Al-Salem et al. 2002).

Several studies linked hyperhomocysteinemia to subclinical atherosclerosis (Svenungsson, Jensen-Urstad et al. 2001; Von Feldt, Scalzi et al. 2006; Von Feldt 2008). Roman et al prospectively studied a cohort of SLE patients with matched controls and determined carotid IMT scores as well as the presence of plaque. Over a period of approximately 3 years of follow-up, 28% of the patients had progressive atherosclerosis, defined as a higher plaque score (new plaque or more extensive plaque). Determinants of atherosclerotic progression after multivariate analysis were patient age at diagnosis, disease duration, and baseline homocysteine concentration. Lupus patients with stable plaque and progressive plaque

were different only in baseline homocysteine concentration (Roman, Crow et al. 2007). A recent study by Perna et al implied a relationship of both asymmetric dimethylarginine and homocysteine to arterial stiffness, but not to the presence or extent of carotid atherosclerosis (Perna, Roman et al. 2010). In the Rho et al study, homocysteine levels in SLE patients were linked to macrophage activation, reflected by increased serum neopterin concentrations. Neopterin (marker of monocyte and macrophage activation associated with atherosclerosis and CV risk in the general population) was associated with atherogenic mediators of inflammation and homocysteine in SLE, but not with coronary atherosclerosis (Rho, Solus et al. 2011).

SS

No data to date regarding the role of homocysteine in the pathogenesis of CV disease in the setting of Sjogren's syndrome is available.

4. Disease related contributors of atherosclerosis in systemic autoimmune diseases

SLE

A number of studies evaluated specific disease parameters and their effect on atherosclerotic disease in SLE patients. Disease duration appears to be an important factor in CVD development. An inverse relationship between SLE activity and plaque size was reported by Manzi et al and longer disease duration was independently associated with carotid plaque (Manzi, Selzer et al. 1999) and coronary calcium scores (Von Feldt, Scalzi et al. 2006). In a cross-sectional and in a longitudinal study, Roman *et al.* found that longer disease duration and higher Systemic Lupus International Collaborative Clinics (SLICC) damage index were independent predictors of carotid plaque formation (Roman, et al. 2003; Roman, et al. 2007). In another report, SLE specific variables were associated with aortic stiffness and included older age, hypertension, higher C3 levels, lower white blood cell count, higher insulin levels, and renal disease (Selzer, Sutton-Tyrrell et al. 2004).

Rua-Figueroa et al who assessed the changes in carotid IMT and the associated risk factors in patients with lupus in a two year period, identified basal measurement IMT, age at diagnosis, homocysteine, C3 and C5a as risk factors for IMT progression (Rua-Figueroa, Arencibia-Mireles et al. 2010). In accord with the previous findings, Haque et al compared SLE patients with verified clinical CV disease (myocardial infarction or angina pectoris) to patients without clinical CV disease. Male sex, older age, increased SLICC damage index, prior use of corticosteroids and azathioprine and more exposure to all classic CV risk factors were positively correlated with clinical CV disease (Haque, Gordon et al. 2010). In our SLE cohort, IMT and the presence of plaque were both statistically significant associated with age, hypertension, triglyceride levels and SLICC damage index score and only plaque with the levels of C3 and C4 (Giannelou 2011).

The role of SLE activity in the formation of non calcified coronary plaque (NCP) was investigated by Kiani et al.; unlike coronary calcium, which is not associated with SLE activity measures or with active serologies, NCP is more common in patients with active disease (Kiani, Vogel-Claussen et al. 2010). Additionally, the presence of lymphopenia and higher levels of serum creatinine and CRP seem to be disease related risk factors in the progression of carotid IMT in juvenile-onset SLE as demonstrated by Huang et al (Huang, Chung et al. 2009).

Although under normal conditions vascular damage is expected to be coupled by acceleration in repair of the endothelium, SLE patients have decreased numbers of circulating EPCs and aberrant function of cells involved in the vascular repair. In particular, lupus EPCs/CACs (myeloid circulating angiogenic cells) have decreased capacity to differentiate into mature ECs and synthesize decreased amounts of the molecules vascular endothelial growth factor and hepatic growth factor (Rajagopalan, Somers et al. 2004; Denny, Thacker et al. 2007; Lee, Li et al. 2007; Moonen, de Leeuw et al. 2007; Westerweel, Luijten et al. 2007). IFN α -a central mediator in lupus pathogenesis- has been recently suggested as a major player of impaired vasculogenesis and atherogenic risk in lupus patients through transcriptional repression of proangiogenic IL-1 pathways, enhancement of foam cell formation, and platelet activation (Lood, Amisten et al. 2010; Thacker, Berthier et al. 2010; Li, Fu et al. 2011).

Autoantibodies including antiOxLDL, AECAs (anti-endothelial cell antibodies) and antibodies against heat shock proteins and phospholipids (APLs) have been linked to lupus related CV disease. In regard to the role of the latter in the pathogenesis of CV disease in the setting of lupus, current evidence is rather conflicting. While in a multiethnic US cohort of patients with SLE, APLs were identified as an independent predictor of CV, cerebrovascular or peripheral vascular events (Toloza, Uribe et al. 2004), such an association has not been detected in three distinct large SLE cohorts (Manzi, Meilahn et al. 1997; Roman, Shanker et al. 2003; McMahon, Grossman et al. 2009). On the other hand, the presence of positive lupus anticoagulant or anti- β 2glycoprotein-I antibodies have been also linked to development of myocardial infarction (Petri 2004). In lupus patients without previous CV history, the occurrence of a first ever CVE (defined as ischemic heart, cerebrovascular peripheral vascular disease or death due to CV disease) was dependent on the presence of positive APLs, markers of endothelial activation/damage advanced age and absence of thrombocytopenia (Gustafsson, Gunnarsson et al. 2009). Proposed mechanisms of APL related CV risk include inhibition of binding of annexin A5 (a protein shown to inhibit to plaque rupture) to the endothelium or reduction of the activity of the atheroprotective enzyme PON1 (Cederholm, Svenungsson et al. 2005) (Delgado Alves, Ames et al. 2002).

The role of anti-OxLDLs has not been yet clarified. In the general population, it is indicated that some aOxLDLs are decreased in the early stage of atherosclerosis development in non autoimmune disease but raised at later stages and in more advanced disease (Lopes-Virella, Virella et al. 1999; Wu, de Faire et al. 1999; Hulthe, Wiklund et al. 2001; Karvonen, Paivansalo et al. 2003). Anti-OxLDL antibodies have been detected in up to 80% of SLE patients with aPS (Vaarala, Alfthan et al. 1993), but no association with thrombosis has been identified (Aho, Vaarala et al. 1996).

In another report by Svenungsson et al anti-OxLDL antibodies were more common in SLE patients with a history of CV disease than in SLE controls or normal subjects (Svenungsson, Jensen-Urstad et al. 2001); titers of anti-OxLDL have been also found to be correlated with anti-double-stranded DNA antibody titres, complement activation and disease activity scores in patients with SLE (Gomez-Zumaquero, Tinahones et al. 2004). Of interest, increased atherosclerotic disease has been attributed to the presence of complexes of oxidized low-density lipoprotein/ β 2 glycoprotein 1 (oxLDL/ β 2GPI) and anti-complex IgG as well as IgM often in association with renal involvement and history of previous thromboembolic episodes (Bassi, Zampieri et al. 2009).

Finally, autoantibodies to endothelial cell (AECAs) and heat shock proteins have been proposed as potential mediators of atherosclerotic risk in lupus patients. (George, Harats et

al. 1999; Mandal, Foteinos et al. 2005). AECAs are associated with lupus disease activity and vasculitis and can act directly on endothelial cells by promoting their activation (Margutti, Matarrese et al. 2008).

RA

Over the last decade, the inflammatory and immunologic mechanisms in the initiation and progression of atherosclerosis (Van Doornum, McColl et al. 2002) have become the focus of particular research interest. Pro-inflammatory cytokines such as TNF- α and IL-6 are released into the systemic circulation and have multiple effects on distant organs including the endothelium and the formation of the atherosclerotic plaque through upregulation of adhesion molecules such as vascular cellular adhesion molecule (VCAM), inhibiting of endothelial nitric oxide (eNOS) production and induction of formation of oxidized LDL (de Groot, Posthumus et al. 2010). Blockade of TNF- α in RA reduces cytokine levels, leucocyte trafficking and platelet levels which may all promote atherosclerotic complications (Full, Ruisanchez et al. 2009). A recently identified new player in atherosclerosis pathogenesis is the macrophage migration inhibitory factor (MIF) which induces the pro-inflammatory mediators TNF- α , IL-1, IL-6 and metalloproteinases (MMPs), activates T cells and promotes angiogenesis. In mice with advanced atherosclerosis, MIF blockade led to plaque regression and reduced monocyte and T-cell content in the plaques (de Groot, Posthumus et al. 2010). The increased arterial stiffness found in RA patients is significantly correlated with disease duration and inflammatory markers such as CRP and IL-6 (Tabas, Williams et al. 2007). As the atherosclerotic plaque matures, the apoptosis of cells in the plaque leads to extracellular lipid accumulation and cellular debris formation. Under the influence of macrophage proteinases, the fibrous cap of the plaques weakens, ruptures and secondary thrombosis may occur (de Groot, Posthumus et al. 2010).

In RA patients, genetic regulation of inflammation seems to be implicated in pathogenesis of accelerated atherosclerosis. Carriers of the allele IL-6-174 -found to be associated with higher IL-6 levels- demonstrated increased prevalence of CV disease (Panoulas, Douglas et al. 2009). In another study by Gabriel et al, inflammatory indicators such as high erythrocyte sedimentation rate (ESR), swelling of small and large joints, rheumatoid nodules, vasculitis and rheumatoid lung disease were all statistically significantly associated with an increased of CV death after adjusting for the above mentioned traditional CV risk factors (Gabriel 2010). Moreover, in patients with RA, the disease activity scale (DAS) was inversely correlated with the number of circulating EPCs, which are hematopoietic stem cells involved in vascular repair, suggesting an additional mechanism of atherogenesis in these patients (Pakozdi, Besenyei et al. 2009; Szekanecz and Koch 2010). Similarly, in patients with lupus, increased levels of circulating apoptotic ECs were correlated with lupus disease activity and endothelial dysfunction.

Serum concentration of autoantibodies in RA, specifically anti-modified citrullinated vimentin (anti-MCV) and anti-cyclic citrullinated peptide (anti-CCP) were found to be positively correlated with disease activity including hsCRP, IL-6, homeostasis model assessment for insulin resistance (HOMA-IR) index, serum levels of rheumatoid factors and IMT score. While anti-MCV and anti-CCP3 are equally sensitive in diagnosing early RA, the former appears to be very useful for monitoring associated subclinical atherosclerosis in early RA (El-Barbary, Kassem et al. 2011).

SS

Associations between signs of subclinical atherosclerosis with the presence of leukopenia, specific autoantibodies (RF, anti-SSA, anti-SSB), articular involvement and parotid gland enlargement, may suggest that immune dysregulation could contribute to the increased risk for atherosclerosis in pSS patients. In our SS cohort, subclinical atherosclerosis –detected by IMT determination- was associated with higher levels of salivary gland infiltration, reduced salivary flow as well as with the presence of SS specific autoantibodies (unpublished results)(Gravani et al, 2011), implying that SS related poor dental hygiene along with immune hyperactivity could contribute to the higher risk for atherosclerotic disease (Mattila, Nieminen et al. 1989)

Finally, circulating CD4+, CD28- cells –previously associated with atherosclerotic risk- did not differ between pSS patients and controls. However, pSS patients demonstrated higher levels of AECAs, (IgG and IgM), and sTM (soluble thrombomodulin), but lower levels of anti-Hsp60 (IgG and IgM) compared to their healthy counterparts, whereas anti-Hsp65 and anti-oxLDL antibody levels were similar in both groups (Vaudo, Bocci et al. 2005) (Gerli, Vaudo et al. 2010).

5. Conclusion

The increased prevalence of CV disease is well established in autoimmune diseases even after correction of the traditional risk factors. Several associations with disease related clinical or serological features, immunologic profile and proinflammatory cytokines are reported. Further investigation is needed to determine a yet unidentified, possibly disease specific mechanism in autoimmune patients.

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7. References

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