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# The prevalence and relevance of traditional cardiovascular risk factors in primary Sjögren's syndrome

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## ABSTRACT

*Accelerated atherosclerosis is a distinct feature of some inflammatory and autoimmune disorders and several specific autoimmune mechanisms and persistent inflammation have been identified to exert a pivotal role in precocious atherosclerotic damage in these disorders. Although increased atherosclerotic risk has been well established in some rheumatic autoimmune systemic diseases, such as systemic lupus erythematosus and rheumatoid arthritis, reliable data regarding the prevalence and pathogenetic mechanisms associated with increased atherosclerotic damage in primary Sjögren's syndrome are scarce. Indeed, primary Sjögren's syndrome is an autoimmune disorder characterised by chronic inflammation and autoimmune dysregulation that shares many pathogenic mechanisms and clinical features with systemic lupus erythematosus and rheumatoid arthritis. Higher prevalence of subclinical atherosclerosis has been observed in primary Sjögren's syndrome patients and recent population-based studies demonstrated an increased risk of cardiovascular events in these patients in comparison to general population. Among mechanisms associated with atherosclerotic damage, the prevalence and the role of traditional cardiovascular risk factors have been poorly investigated. In particular, the issue of whether the presence of these cardiovascular risk factors is associated with an increased risk of cardiovascular events needs to be further explored.*

## Introduction

Systemic autoimmune diseases (ADs) are now recognised as independent risk factors for atherosclerotic disease and represent interesting models to investigate the intriguing relationship between chronic inflammation, autoimmunity

and atherosclerosis. The increased incidence of cardiovascular (CV) events occurring in these patients, often at young age, and the higher mortality for CVD characterising ADs confirm the strict association between accelerated atherosclerosis and CV morbidity and mortality. In the last years, multiple mechanisms have been hypothesised to contribute to the pathogenesis of precocious vascular damage in ADs, but several issues remain yet to be fully clarified (1, 2). Undoubtedly, innate and adaptive inflammatory and immune-mediated mechanisms characterising the pathogenesis of systemic ADs play an established role also in the induction and perpetuation of vascular atherosclerotic damage. Indeed, atherosclerosis is now considered a chronic disease where both innate and adaptive immuno-inflammatory mechanisms are involved and inflammation is pivotal at all stages of the atherosclerotic damage. Pro-inflammatory cytokines, adhesion molecules, disease-specific autoantibodies and chronic inflammation strictly interact in a complex pathogenic mechanism leading to endothelial dysfunction, organic damage of arterial wall and plaque formation and rupture (3). On the other hand, it is also undeniable that these mechanisms do not fully explain the increased CV risk in these diseases, implying that other factors contribute to the CV burden seen in these patients.

In the general population, traditional CV risk factors exert a pivotal role in the pathogenesis of CV damage and valuation of CV risk and the main risk stratification algorithms are based on presence of well-established CV risk factors, like cholesterol levels, cigarette smoking, diabetes mellitus (DM) and blood pressure. On the other hand, risk calculators designed for use in the general population do not accurately

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estimate the risk of CVD in patients with chronic inflammatory and ADs, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and none of these CVD risk prediction algorithms is ideal (4). A major point limiting the feasibility of CV risk calculators in the estimation of CV morbidity and mortality in these patients is the difficulty to quantify the significant contribution of chronic inflammatory burden and immune system deregulation to the atherosclerotic damage of arterial wall. Moreover, it is relevant to consider that classical risk factors for CVDs are more prevalent in patients with ADs and have a different weight in the pathogenesis of vascular damage in comparison to the general population. Therefore, the evaluation of the real prevalence of traditional CV risk factors in patients with systemic ADs in comparison to the general population and the analysis of their contribution to CVD represent two unmet medical needs.

Among the whole spectrum of systemic ADs, SLE and RA have the strongest evidence and the largest body of literature supporting the increased prevalence of CVD and the higher risk of CV mortality in these patients (1, 2). Recently, however, a meta-analysis of observational cohort studies demonstrated that also primary Sjögren's syndrome (pSS), a disease mainly affecting women in middle age, is characterised by nearly one and a half-fold increased risk of both CVD, including coronary artery disease, acute coronary syndrome, myocardial infarction, angina and ischaemic heart disease, and cerebrovascular events, namely stroke and cerebrovascular infarction, in comparison to control subjects (5). Indeed, pSS is a chronic immune-mediated inflammatory disease characterised by glandular and systemic manifestations sharing many clinical and autoimmune similarities with RA and SLE and represents an interesting model to investigate the pathogenesis of precocious atherosclerosis in ADs (6). In particular, the disease is characterised by a slow and benign evolution, often not requiring immunosuppressive therapies or high dose corticosteroid

treatment, thus allowing the analysis of the direct effect of autoimmunity and chronic inflammation on atherosclerosis without the interference of chronic therapies (7, 8).

In ADs, subclinical functional and structural changes of the arterial wall have been demonstrated to occur early in the course of the disease and, probably, precede CV events (9). Similarly, in pSS, increased prevalence of both functional and organic subclinical atherosclerotic damage has been demonstrated by different instrumental methods, including endothelial dysfunction by flow- and nitrate-mediated vasodilation, aortic stiffness by pulse wave velocity, organic damage of the arterial wall by intima-media thickness, left ventricular dysfunction and assessment of coronary flow reserve (10). The direct vascular damage arises from a strict interplay between disease-related chronic inflammatory background and disease-specific autoimmune markers and both systemic inflammation and immune dysregulation represent key components in atherogenesis (3). This is also evident in pSS where both inflammatory factors, including C reactive protein, adhesion molecules and inflammatory-specific disease manifestations, like parotid swelling and joint involvement, and immune markers, like anti-SSA/Ro or SSB/La antibodies, have been demonstrated to be significantly associated with atherosclerotic damage (11-15). In this setting, it is fascinating the demonstration that pSS itself emerges as an independent risk factor for arterial wall thickening independently from age, sex, hypertension (HTN), smoke and lipid levels (16, 17). On the other hand, the role and contribution of traditional CV risk factors in the pathogenesis of subclinical atherosclerosis and in the increased risk of clinically manifested CV events represent a research area yet to be explored. In RA and SLE, studies analysing the actual prevalence of traditional CV risk factors in comparison to the general population reported conflicting evidence mainly due to study design, definition and assessment of CV risk factors and features of enrolled population. However, traditional CV risk factors and disease characteris-

tics are consistently related to vascular haemodynamic alterations and CV disease outcome in RA (18, 19). Similarly, increased prevalence of traditional CV risk factors, including metabolic syndrome, HTN, increased body mass index (BMI), has been detected in SLE patients and has been associated to increased risk of CV events during disease course (20, 21).

In recent years, three large population-based cohort studies demonstrated a higher prevalence of some traditional CV risk factors in pSS patients in comparison to general population, thus explaining, at least in part, the higher risk of CV events demonstrated in these patients (22-24). On the other hand, smaller case-control studies reported conflicting results and many factors, including methodologic issues, study design, traditional CV risk factor assessment and definition and disease features, may partially explain such discrepancy. Moreover, the actual importance of traditional CV risk factors in the determination of increased the risk of CV events in these patients is unknown. Undoubtedly, awareness of the clinical relevance of traditional CV risk factors on CV events represents essential to individualise CV disease risk evaluation and prevention for pSS patients.

Consequently, the aim of the paper was to analyse the prevalence and impact of traditional CV risk factors on CV risk in patients with pSS.

## **The role of traditional cardiovascular risk factors**

### *Hypertension*

Among the traditional CV risk factors, HTN has the highest incidence and prevalence both in chronic inflammatory diseases, like RA and ankylosing spondylitis, and in systemic ADs, including SLE, systemic sclerosis and inflammatory bowel diseases (24, 25). Indeed, in these patients, HTN is a major traditional CV risk factor and its prevalence is increased in comparison to general population. Furthermore, disease-related factors, including inflammation and disease-specific treatment, can coincide with the appearance of HTN, and HTN is an important factor promoting

the progression of atherosclerosis. This strict relationship may be explained, at least in part, by shared inflammatory and innate and adaptive immune-mediated pathogenic mechanisms underlying the two conditions. Indeed, arterial wall injury as a consequence of hypertensive stimuli induces activation of inflammatory cytokines with local recruitment of inflammatory cells, toll-like receptors recruitment on arterial wall and complement and innate immune system activation, thus driving the pathology of arterial HTN and hypertensive end-organ damage (24, 25). Moreover, in these patients, increased blood pressure is associated with subclinical atherosclerosis, asymptomatic CV damage with left ventricular dysfunction and, of note, with higher risk of CV events, including myocardial infarction, congestive heart failure and cerebrovascular events, in comparison to normotensive patients (24, 25). The relevant impact of HTN on overt CVD in these patients is further strengthened by the evidence that patients with HTN experience CV events mainly in the first years after the diagnosis, thus suggesting the importance of appropriate control of blood pressure values in patients with systemic ADs.

As depicted in Table I, HTN represents a main CV risk factor also in pSS. The prevalence of HTN in these patients ranges from 13% to 52% and, in some studies, resulted significantly increased in comparison to control subjects (14, 22, 26, 27). Interestingly, the prevalence of HTN resulted significantly increased also in pSS patients aged less than 50 years in comparison to age-matched controls and independently of corticosteroid therapy, suggesting that other disease-related pathogenic mechanisms, such as genetic, immunologic and/or inflammatory factors, may contribute to blood pressure elevation in these patients (14). In this setting, the lower frequency of HTN detected only in a study involving 312 pSS patients from Spain could be explained by a selection bias of the control population which included patients from primary care in follow-up for prevalent diseases such as HTN (23). Nevertheless, some factors should be considered in the

analysis and interpretation of these results. First of all, the definition of HTN employed in these studies was highly variable and these differences may partly explain the discrepancy of the results and the high variability of HTN prevalence among studies. Systemic HTN was defined by: i) systolic blood pressure  $\geq 130$  mmHg and/or diastolic blood pressure  $\geq 85$  mmHg and/or current use of antihypertensive medications (26, 28, 29); ii) physician diagnosis and/or prior/active antihypertensive medication (22, 23); iii) systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg (14, 17, 30, 31); iv) ICD-code definition (27). Moreover, the different ethnicity of patients enrolled may affect the variable prevalence of HTN among studies (32), as well as other concomitant factors such as reduced physical activity related to the chronic disease and use of certain medications. Finally, the sex bias represents an adjunctive relevant factor to consider in the analysis of data. Indeed, pSS affects nearly exclusively middle-aged female and gender differences in cardiac adaptation to blood pressure have been demonstrated. In particular, women with HTN have higher prevalence of left ventricular hypertrophy in comparison to males and a lower change of left ventricular functional parameters after introduction of antihypertensive therapy (33). Effects of sex-related hormonal changes may, at least in part, account for this phenomenon, in particular in middle-aged women in relation to menopausal status. Oestrogens have significant effects on the CV system and oestrogen receptors in the ventricular myocardium affects the cellular physiology of cardiac tissues. Among female population, menopause is significantly associated with higher left ventricular mass and interventricular septum thickness, indicating that sex hormones may play an important role in unfavourable ventricular remodelling and higher risk of elevated blood pressure (33). However, cardiac functional and structural changes in pSS and their effect on CV risk factors are still to be explored.

Of more importance, among all traditional CV risk factors, HTN seems to

exert the most relevant effect on CV outcome in these patients. As illustrated in Table II, HTN or mean arterial pressure are significant predictor, at multivariate analysis and after adjusting for other risk factors, of increased prevalence of subclinical atherosclerosis, namely carotid plaque and arterial stiffness (17, 34), and of higher risk of CV events, including ischaemic heart disease, stroke and peripheral artery disease (14, 23, 27), thus suggesting that HTN represents a major contributing factor to the increased risk of CV events in pSS patients. This is an important point to address, in consideration that, also demonstrated in RA, HTN is underdiagnosed and suboptimally treated in pSS patients (14, 24).

#### *Diabetes mellitus*

As observed for HTN, the prevalence of DM in pSS is characterised by a wide variability, ranging from 0% to 28% (Table I). In some studies, the prevalence of DM resulted significantly higher in comparison to control subjects (23, 27, 35) while only one population-based study demonstrated a lower frequency of DM in pSS patients in comparison to healthy subjects (22). As observed for HTN, the different definition and assessment of DM among the studies may largely explain the wide prevalence range. Indeed, DM was defined by: i) presence in at least 2 determinations of fasting glycaemia  $>126$  mg/dl (35); ii) physician diagnosis of diabetes requiring insulin or hypoglycaemic agents and/or presence in at least two determinations of fasting glycaemia higher than 126 mg/dL (17, 22, 23, 31); iii) fasting glucose ( $\geq 100$  mg/dL) and/or drug therapy for hyperglycaemia (26); iv) assessment from medical records and clinical consultation (14) v) ICD-code definition (27). Moreover, the higher prevalence of DM was observed in two cohorts of Spanish pSS patients (23, 35), thus suggesting the importance of genetic and metabolic background, dietary intake, lifestyle habits and local guidelines for DM screening. Nevertheless, the association between pSS and DM has been demonstrated both in experimental and clinical studies and reinforces the hypothesis of

**Table I.** Prevalence of traditional CV risk factors in case-controls studies in pSS patients.

| Author (Ref)<br>Country    | Pts N.<br>(sex)  | Age<br>yrs           | DD<br>yrs           | HTN<br>(%) | DM<br>(%) | Smoke<br>(%) | BMI<br>kg/m <sup>2</sup> | TC<br>mg/dl                         | HDL<br>mg/dl         | LDL<br>mg/dl           | TG<br>mg/dl           |
|----------------------------|------------------|----------------------|---------------------|------------|-----------|--------------|--------------------------|-------------------------------------|----------------------|------------------------|-----------------------|
| Vaudo (11)<br>Italy        | 37<br>(100% F)   | 48±14                | 7 (1-15)<br>median  | 22         | 3         | 21           | 22±5                     | 182±35                              | 50±12*               | 120±31                 | 97±44                 |
| Ramos-Casals (35)<br>Spain | 254<br>(92% F)   | 52±1                 | 136±4<br>months     | NA         | <b>28</b> | NA           | NA                       | 34%<br>>250                         | NA                   | NA                     | <b>28%</b><br>>150    |
| Rachapalli (30)<br>UK      | 25<br>(96% F)    | 62±9                 | 9±3                 | 52         | Ex        | NA           | NA                       | 8%<br>HyperC <sup>‡</sup>           | NA                   | NA                     | NA                    |
| Gerli (13)<br>Italy        | 45<br>(100% F)   | 44±8                 | 8±5                 | 13         | 0         | 18           | 23±4                     | 190±46                              | 50±15*               | 120±39                 | 115±35                |
| Perez-De-Lis (23)<br>Spain | 312<br>(95% F)   | 55±1                 | NR                  | 30*        | <b>27</b> | 19*          | 18% obesity#             | 30%<br>>250                         | 10%<br>< 40          | 21%<br>>160            | <b>22%</b><br>>150    |
| Zardi (28)<br>Italy        | 18<br>(100% F)   | 70 (65-79)<br>median | 7 (6-10)<br>median  | 39         | 0         | 17           | 26 (21-34)<br>median     | 201(172-248)<br>median              | 57 (25-89)<br>median | 121 (83-141)<br>median | 123(85-216)<br>median |
| Juarez (14)<br>UK          | 538<br>(100% F)  | 59±12                | NR                  | <b>38</b>  | 3         | 4*           | 20%<br>≥30               | <b>18%</b><br>≥240                  | 13%<br><40           | 13%<br>≥160            | <b>24%</b><br>≥150    |
| Atzeni (46)<br>Italy       | 22<br>(73% F)    | 60±8                 | 46±8<br>months      | Ex         | Ex        | Ex           | 24±5                     | NR                                  | NR                   | NR                     | NR                    |
| Gravani (16)<br>Greece     | 64<br>(F/M 15:1) | 57±12                | 8±7                 | 36         | 6         | 8±17§        | 27±5                     | 195±34*                             | 55±14                | 120±30*                | 103±43                |
| Sabio (31)<br>Spain        | 44<br>(100% F)   | 52 (44-56)<br>median | 6 (3-9)<br>median   | 30         | 7         | 23           | 25 (23-27)<br>median     | 9%<br>≥240                          | 69 (51-83)<br>median | 101*(87-128)<br>median | 14%<br>≥ 150          |
| Bartoloni (22)<br>Italy    | 778<br>(100% F)  | 56±10                | 5±6                 | <b>32</b>  | 4*        | 13*          | 11%*<br>≥30              | <b>30%</b><br>HyperC <sup>‡</sup>   | NA                   | NA                     | NA                    |
| Balarini (17)<br>Brazil    | 63<br>(75% F)    | 50±11                | 111±76<br>months    | 40         | 10        | 3            | 26±4                     | 181±30*                             | 51±11                | 102±26*                | 135±77                |
| Demirci (34)<br>Turkey     | 75<br>(100% F)   | 54±9                 | 10 (1-23)<br>median | NR         | Ex        | 15           | 29±5                     | 203±33                              | NR                   | 121±32*                | NR                    |
| Zardi (29)<br>Italy        | 25<br>(100% F)   | NR                   | 8<br>median         | 36         | 0         | 0            | 26<br>median             | 196                                 | 62                   | 112                    | 116                   |
| Augusto (26)<br>Brazil     | 71<br>(100% F)   | 48±10                | NR                  | <b>32</b>  | 6         | 4            | 28±6                     | 178±40*                             | 55±16                | 102±32*                | 105±45                |
| Wu (27)<br>China           | 4.175<br>(75% F) | 50±17                | NR                  | <b>23</b>  | <b>12</b> | NA           | NA                       | <b>17%</b><br>Hyperlip <sup>‡</sup> | NA                   | NA                     | NA                    |

Values are mean±SD unless indicated otherwise. Statistically significant values vs. controls are in bold. \*Lower vs. controls. § packs/year. # waist circumference >102 cm for men and >88 cm for women. † total cholesterol to high-density lipoprotein cholesterol ratio >5. ‡TC > 240 mg/dl in ≥ 3 assays. ‡ICD-9 code: 272. Ex: exclusion criteria. Pts: patients; yrs: years; DD: disease duration; HTN: hypertension; DM: diabetes mellitus; BMI: body mass index; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; F: female; M: male; NA: not assessed; NR: not reported; HyperC: hypercholesterolaemia; Hyperlip: hyperlipaemia.

an autoimmune common background characterising the two diseases (36, 37). On the other hand, the magnitude of the difference between studies (0-10% versus 27-28%) warrants further investigation. In this setting, it may be argued that the low prevalence of DM detected in the majority of the studies, sometimes significantly reduced in comparison to general population (22), suggests a protective effect of antimalarials, commonly employed in these patients (35), or may be ascribed to the lower dose of corticosteroid therapy used in pSS in comparison to other sys-

temic ADs, such as SLE or RA. Interestingly, diabetic pSS patients are older at the diagnosis, have lower frequency of positive anti-nuclear antibodies and are characterised by a more aggressive disease, with increased risk of systemic involvement and disease-related vasculitic manifestations (Raynaud's phenomenon, vasculitis), suggesting that this metabolic alteration may contribute to trigger inflammatory process and vascular damage in pSS (35). The presence of DM, however, does not appear to exert a significant impact on CV outcome in these patients (Table II).

### Dyslipidaemia

An impaired lipid profile, mainly characterised by normal or increased total cholesterol, increased triglyceride and reduced high-density lipoprotein (HDL) levels, represents a major finding in pSS patients, as also widely demonstrated in SLE and RA patients (Table I) (25). Notably, many studies showed significantly reduced levels of low-DL (LDL) cholesterol in patients in comparison to control subjects (16, 17, 26, 31, 34). However, data are scarcely comparable due to the different definitions of hypercholesterolaemia.

**Table II.** Predictors of subclinical atherosclerosis and of CV events at multivariate analysis.

| Author (Ref)<br>Country    | Pts<br>sex       | DD<br>yrs           | GC<br>therapy | IS<br>therapy     | Subclinical<br>ATS              | CV<br>events        | Traditional CV<br>risk factors  | Immunologic factors                      | Other disease-related<br>factors |
|----------------------------|------------------|---------------------|---------------|-------------------|---------------------------------|---------------------|---------------------------------|--|----------------------------------|
| Vaudo (11)<br>Italy        | 37<br>(100% F)   | 7 (1-15)<br>median  | 54%<br>former | HCQ<br>40%        | c/f IMT<br>Plaque*              |                     |                                 | Anti-SSA<br>(c/f IMT)                    | Leukopenia<br>(f IMT)            |
| Rachapalli (30)<br>UK      | 25<br>(96% F)    | 9±3                 | NR            | NR                | ABI                             | NA                  |                                 |  | Disease duration                 |
| Gerli (13)<br>Italy        | 45<br>(100% F)   | 8±5                 | 38%<br>former | HCQ 24%           | FMV<br>NMV                      |                     |                                 | Anti-SSB, RF (NMV)                       | VCAM-1,<br>leukopenia (NMV)      |
| Perez-De-Lis (23)<br>Spain | 312<br>(95% F)   | NR                  | 41%           | HCQ 24%<br>IS 14% |                                 | IHD, stroke,<br>PAD | HTN<br>HDL < 40 mg/dl           |  |                                  |
| Zardi (28)<br>Italy        | 18<br>(100% F)   | 7 (6-10)<br>median  | 0%            | 0%                | c IMT <sup>o</sup>              | NA                  |                                 |  |                                  |
| Juarez (14)<br>UK          | 538<br>(99% F)   | NR                  | 10%           | HCQ 30%<br>IS 6%  |                                 | MI<br>stroke        | HTN<br>(all pts with CV events) | Anti-SSA/SSB<br>(all pts with CV events) |                                  |
| Atzeni (46)<br>Italy       | 22<br>(73% F)    | 46±8<br>months      | 32%           | HCQ NR<br>IS 45%  | CFR, cIMT <sup>§</sup> ,<br>PWV | NA                  |                                 |  |                                  |
| Gravani (16)<br>Greece     | 64<br>(F/M 15:1) | 8±7                 | NR            | NR                | c/f IMT<br>Plaque*              |                     | Age<br>(c/f IMT, plaque)        |  |                                  |
| Sabio (31)<br>Spain        | 44<br>(100% F)   | 6 (3-9)<br>median   | 21%           | HCQ 34%<br>IS 23% | cfPWV                           | NA                  | MetS                            |  | SSDI<br>FRS                      |
| Bartoloni (22)<br>Italy    | 1343<br>(96% F)  | 5±6                 | 45%           | HCQ 45%<br>IS 18% |                                 | MI, HF<br>stroke    |                                 |  | CNS involvement<br>GC/IS therapy |
| Balarini (17)<br>Brazil    | 63<br>(75% F)    | 111±76<br>months    | 32%           | HCQ<br>40%        | Carotid<br>plaque <sup>§</sup>  |                     | HTN<br>HyperTG                  |  |                                  |
| Demirci (34)<br>Turkey     | 75<br>(100% F)   | 10 (1-23)<br>median | 14%           | IS<br>10%         | cfPWV                           |                     | MAP, LDL levels                 |  |                                  |
| Zardi (29)<br>Italy        | 25<br>(100% F)   | 8<br>median         | 0%            | 0%                | c IMT <sup>o</sup>              | NA                  |                                 |  | Disease duration                 |
| Wu (27)<br>China           | 4,175<br>(75% F) | NR                  | 11%           | HCQ, IS<br>16%    |                                 | CHD                 | HTN<br>Hyperlip                 |  | SS, age, male sex                |

Values are mean (±SD) unless indicated otherwise.

Pts: patients; yrs: years; DD: disease duration; GC: glucocorticoid; IS: immunosuppressive; ATS: atherosclerosis; CV: cardiovascular; c/f: carotid/femoral; IMT: intima-media thickness; FMV: flow-mediated vasodilation; NMV: nitrate-mediated vasodilation; RF: rheumatoid factor; MAP: mean arterial pressure; ABI: ankle brachial index; HTN: hypertension; VCAM-1: vascular cell adhesion molecule-1; SSDI: Sjögren's syndrome damage index; MI: myocardial infarction; IHD: ischaemic heart disease; HF: heart failure; PAD: peripheral artery disease; CHD: chronic heart disease; FRS: Framingham risk score; MetS: metabolic syndrome; CNS: central nervous system; Hyperlip: hyperlipaemia; HyperTG: hypertriglyceridaemia; LDL: low-density lipoprotein; SS: Sjögren's syndrome.

\*Arterial wall thickening: mean carotid IMT > 0.90 mm. Plaque: focal protrusion > 50% of the surrounding wall.

<sup>o</sup>Protrusion into the lumen > 0.5 mm or a protrusion into the lumen > 50% of IMT at adjacent area or IMT ≥ 1.5 mm

<sup>§</sup>Distance between the leading edges of the lumen interfaces and the media/ adventitia interface of the far wall.

<sup>o</sup>Distance between the interface of the complex "media-adventitia" and the interface of the complex "lumen-intima".

mia employed and because many studies analysed mean fasting lipid values without calculating the prevalence of hypercholesterolaemia, hypertriglyceridaemia, high LDL and low HDL using established definitions (Table I).

In fact, mechanisms underlying the altered lipid profile in pSS are quite complex and represent an intriguing field to explore. Disease-related immunologic and inflammatory features have been demonstrated to be associated with the impaired lipid profile in pSS. In particular, pSS patients with circulating anti-SSA/SSB antibodies are charac-

terised by lower total cholesterol and HDL levels (12, 38). Higher frequency of antinuclear antibody positivity, a marker of immune system hyperactivity, and higher levels of erythrocyte sedimentation rate, which reflects a chronic inflammatory state, have been demonstrated in pSS subjects with dyslipidaemia and hypertriglyceridaemia, respectively, compared to normolipidaemic patients (14, 39). Moreover, total cholesterol and HDL levels have been associated with increased immunoglobulin G serum concentration, which is an indirect marker of B

lymphocyte hyperactivity (11), further strengthening the close relationship between disease-specific immunologic background and impaired lipid profile. In contrast, hypertriglyceridaemia seems to be mainly related to a differentiated clinical expression of the disease rather than to immunological markers. In particular, higher prevalence of parotid enlargement was observed in hypertriglyceridaemic patients, although the difference was not statistically significant (35) and patients with hypertriglyceridaemia were more likely to have abnormal salivary

flow test findings (14). Izumi *et al.* analysed the main clinical features of 24 patients with sicca syndrome related to dyslipidaemia, including 50 patients with pSS as control group. They found parotid gland enlargement in all patients with hypertriglyceridaemia, but in none of those with hypercholesterolaemia, suggesting a close relationship between parotid gland enlargement and high serum triglyceride levels (40). Finally, the abnormal lipid metabolism represents a factor associated with higher risk of subclinical atherosclerosis and of CV events in these patients (Table II). Hypertriglyceridaemia, reduced HDL, LDL levels and hyperlipaemia resulted significant predictors of accelerated atherosclerosis, in particular of increased aortic stiffness and carotid plaque, as well as of clinically manifested CV events, including ischaemic heart disease, stroke and peripheral artery disease (17, 23, 27, 34). In conclusion, the presence of a specific altered lipid profile in pSS is associated with a pattern of clinical and immunological disease phenotype. As shown in RA, the cause of abnormal lipid profile in pSS may be multifactorial and is yet to be fully explored. It may be hypothesised that the disease itself may cause this altered metabolic profile as a result of the persistent chronic inflammation or that patients with pSS may have a genetic background predisposing to metabolic alterations. In this setting, corticosteroid use does not seem to be associated with increased prevalence of dyslipidaemia in these patients (14) except for higher frequency of DM observed in patients treated with corticosteroids (23, 35).

#### Obesity

As illustrated in Table I, up to 18% of pSS patients were obese according to BMI value. However, mean BMI resulted similar in patients and controls except in a cohort study from Italy where a statistically significant lower prevalence of obesity characterised pSS in comparison to healthy women (22). This may suggest that, as demonstrated in RA, the role of obesity in pSS is complex and that lower BMI may reflect uncontrolled systemic inflam-

mation, thus hypothesising also in these patients the paradoxical association between low BMI and increased risk of CV events. Nevertheless, it is important to consider that metabolic syndrome, reflecting a clustering of traditional and metabolic CV risk factors including obesity and visceral adiposity, insulin resistance, dyslipidaemia and hypertension, is now recognised as an important CV risk factor in pSS (26). Primary SS patients with metabolic syndrome have higher BMI, waist circumference and body fat mass, reflecting central obesity, in comparison to patients without metabolic syndrome (26). Interestingly, the pSS patients with metabolic syndrome had greater serum levels of leptin and interleukin-1 $\beta$  in comparison to the other group, suggesting a close relationship between chronic inflammation, characterised by the production of interleukin-1, and visceral obesity and insulin resistance, which are associated with leptin production (26). Moreover, a number of metabolic syndrome criteria was associated with arterial stiffness measured by pulse wave velocity, suggesting a direct involvement of this metabolic alteration on incident atherosclerosis in pSS patients (31).

#### Smoke

The proportion of current smokers in the pSS groups is globally lower than that in the general population and this has been related to the exacerbation of oral and ocular discomfort by smoking in these patients. It is interesting to note that cigarette smoking exerts a well-recognised adverse effect in patients with some autoimmune diseases; in particular, in RA, smoking represents the main environmental exposure implicated in disease development and progression. On the other hand, smoker patients with pSS do not have an increased risk of extraglandular manifestations and are characterised by lower salivary gland biopsy focus score and lower frequency of anti-SSA/SSB antibody positivity compared to non-smokers (41). However, considering that women with RA are less likely to be smokers in comparison to male patients and that the smoking-related CV risk is lower for women, it may be

hypothesised that smoke represents a minor CV risk factor in women with pSS (42).

#### The interaction between traditional risk factors and disease-specific features

The demonstration that CV risk is increased in pSS even after adjusting for traditional CV risk factors suggests that the disease itself may represent an independent risk factor for CV disease (16, 31). However, the relationship between disease-related inflammatory and autoimmune features, traditional CV risk factors and risk of CV disease needs to be further explored. Large population-based studies demonstrated that higher frequency of traditional CV risk is associated with peculiar disease features in these patients. In particular, Spanish patients with at least three CV traditional risk factors had a different profile characterised by higher frequency of extra-glandular manifestation, in particular liver and central nervous system involvement, higher mean levels of C-reactive protein and received corticosteroids more frequently in comparison to patients without traditional risk factors (23). Interestingly, central nervous system involvement and ever use of glucocorticoid and immunosuppressive therapies, indirect markers of a more aggressive disease, were independent predictors of higher risk of CV events in an Italian cohort (22).

On the other hand, the link between traditional CV risk factors and disease-specific markers of immune system activation requires better clarification. In the same Spanish cohort, presence of at least three traditional CV risk factors was associated with a lower percentage of circulating gamma globulins (23). Similar results were demonstrated in a large Italian cohort where patients without traditional risk factors presented circulating anti-SSA/SSB antibodies, leukopenia, hypergammaglobulinaemia and hypocomplementaemia more frequently than subjects with one or more CV disease risk factors (22). Hypercholesterolaemia was associated with lower frequency of immunological markers such as anti-SSA/SSB antibodies and low C3 and C4 levels in a large

Spanish cohort (35), while pSS Italian patients with circulating anti-SSA/SSB antibodies and leukopenia were characterised by lower total cholesterol and HDL-cholesterol levels in comparison to controls (11, 12).

This suggests that, in pSS patients, CV risk factors may worsen or trigger inflammatory processes in contributing to systemic involvement, while the number of CV risk factors is associated with a poorer disease immunological expression. Further studies are needed to better clarify the role of immunologic profile in the increased CV. Indeed, although anti-SSA and leukopenia are associated with subclinical atherosclerosis (11, 13), no relationship was observed between these autoantibodies and risk of CV events except for higher risk of angina in leukopenic patients in comparison to patients with normal leukocyte count (22, 31).

Nevertheless, other factors may contribute to incident atherosclerosis in these patients. Interestingly, cumulative damage and longer disease duration, reflecting the effect of long-standing systemic inflammation and greater immunologic imbalance, were independently associated with increased risk of subclinical atherosclerosis in these patients (28, 30, 31).

### Conclusions

Optimal management and prevention of traditional CV disease risk factors continues to be an important goal of CV disease risk management in patients with systemic ADs as demonstrated by the relevant importance of these factors in determining the increased risk of CV morbidity and mortality observed in these patients (43). In this setting, pSS represents an interesting and still unexplored model to investigate the role of traditional CV risk factors and their interaction with inflammatory and autoimmune pathogenic mechanisms in determining the increased risk of CV events. As widely demonstrated for other systemic inflammatory and ADs, such as RA, SLE and systemic sclerosis (44), also pSS is associated with increased overall risk of incident atherosclerosis, assessed by different instrumental methods, and of manifested

CV events (5, 10). Moreover, as demonstrated in other ADs, multiple factors concur to the pathogenesis of CV atherosclerotic damage in pSS patients. In this setting, a recent study demonstrated that impaired sleep is associated with a significant higher risk of subclinical atherosclerosis in pSS patients even after adjustment for traditional CV risk factors, thus suggesting that multiple different factors contribute to atherosclerosis in these patients (45). The analysis of available studies suggests that some traditional CV risk factors, namely HTN, hypertriglyceridaemia and metabolic syndrome, are more prevalent in pSS in comparison to age and sex-matched general population and that these factors may exert a role in determining the higher prevalence of subclinical atherosclerotic damage, as detected by impaired endothelial function and coronary flow reserve and by increased intima-media thickness and arterial stiffness. Of great importance, some traditional CV risk factors, in particular HTN and altered lipid profile, seem to be significantly associated with increased risk of CV events, thus suggesting the importance of proper control and management of HTN and dyslipidaemia, in particular hypertriglyceridaemia, in these patients to prevent progression from subclinical atherosclerosis to CV events. However, the evaluation of CV risk profile in these patients is strictly linked to the analysis of disease-related inflammatory and immune markers which have been demonstrated to exert a direct role in atherosclerotic damage and CV morbidity and mortality. In this setting, it is intriguing the demonstration that longer disease duration, disease damage and more active disease with extra-glandular involvement and systemic manifestations are factors to be considered and addressed as potential players in increase CV events. Indeed, it may be speculated that a peculiar disease phenotype characterised by systemic involvement, presence of damage related to a chronic and active disease and specific immunologic profile should be considered at higher risk to develop CV disease and, consequently, more aggressively treated to prevent this risk. In this set-

ting, however, how and to what extent traditional CV risk factors and disease-associated features are correlated with precocious subclinical atherosclerotic damage and CV events need to be more deeply analysed. Furthermore, knowledge of the substantial proportion of CVD risk attributable to disease activity and severity is extremely important in order to reduce the risk of CV events in these patients. Undoubtedly, addressing interaction between chronic inflammation, immune system dysregulation, CV disease and other comorbidities in patients with pSS has to be acknowledged and directly targeted to improve CV prevention. Further studies involving wider number of patients are needed to investigate optimal management of these patients in order to prevent CV mortality and to drive guidelines specifically addressed to proper management of traditional CV risk factor in order to prevent CV events.

### References

1. NAGY G, NÉMETH N, BUZÁS I: Mechanisms of vascular comorbidity in autoimmune diseases. *Curr Opin Rheumatol* 2018; 30: 197-206.
2. SZEKANECZ Z, KERÉKES G, VÉGH E: Autoimmune atherosclerosis in 3D: How it develops, how to diagnose and what to do. *Autoimmun Rev* 2016; 15: 756-76.
3. BARTOLONI E, SHOENFELD Y, GERLI R: Inflammatory and autoimmune mechanisms in the induction of atherosclerotic damage in systemic rheumatic diseases: two faces of the same coin. *Arthritis Care Res* 2011; 63: 178-83.
4. ARTS EE, POPA C, DEN BROEDER AA *et al.*: Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 668-74.
5. YONG WC, SANGUANKEO A, UPALA S: Association between primary Sjögren's syndrome, cardiovascular and cerebrovascular disease: a systematic review and meta-analysis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S190-97.
6. MARIETTE X, CRISWELL LA: Primary Sjögren's syndrome. *New Engl J Med* 2018; 378: 931-9.
7. BALDINI C, PEPE P, QUARTUCCIO L *et al.*: Primary Sjögren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. *Rheumatology* 2014; 53: 839-44.
8. FERRO F, MARCUCCI E, ORLANDI M, BALDINI C, BARTOLONI BOCCI E: One year in review 2017: primary Sjögren's syndrome. *Clin Exp Rheumatol* 2017; 35: 179-91.
9. BARTOLONI E, ALUNNO A, BISTONI O,

- GERLI R: How early is the atherosclerotic risk in rheumatoid arthritis? *Autoimmun Rev* 2010; 9: 701-7.
10. VALIM V, GERDTS E, JONSSON R *et al.*: Atherosclerosis in Sjögren's syndrome: evidence, possible mechanisms and knowledge gaps. *Clin Exp Rheumatol* 2016; 34: 133-42.
  11. VAUDO G, BARTOLONI BOCCI E, SHOENFELD Y *et al.*: Precocious intima-media thickening in patients with primary Sjögren's syndrome. *Arthritis Rheum* 2015; 52: 3890-7.
  12. GERLI R, BARTOLONI BOCCI E, VAUDO G, MARCHESI S, VITALI C, SHOENFELD Y: Traditional cardiovascular risk factors in primary Sjögren's syndrome: role of dyslipidemia. *Rheumatology* 2006; 45: 1581-2.
  13. GERLI R, VAUDO G, BARTOLONI BOCCI E *et al.*: Functional impairment of the arterial wall in primary Sjögren's syndrome: combined action of immunologic and inflammatory factors. *Arthritis Care Res* 2010; 5: 712-8.
  14. JUAREZ M, TOMS TE, DE PABLO P *et al.*: Cardiovascular risk factors in women with primary Sjögren's syndrome: United Kingdom primary Sjögren's syndrome registry results. *Arthritis Care Res* 2014; 5: 757-64.
  15. GARCIA A, DARDIN LP, MINALI PA, CZAPKOWSKY A, AJZEN SA, FERNANDES MOÇA TREVISANI V: Asymptomatic atherosclerosis in primary Sjögren syndrome. Correlation between low ankle brachial index and autoantibodies positivity. *J Clin Rheumatol* 2016; 22: 295-8.
  16. GRAVANI F, PAPADAKI I, ANTYPY A *et al.*: Subclinical atherosclerosis and impaired bone health in patients with primary Sjögren's syndrome: prevalence, clinical and laboratory associations. *Arthritis Res Ther* 2015; 17: 99.
  17. BALARINI GM, ZANDONADE E, TANURE L *et al.*: Serum calprotectin is a biomarker of carotid atherosclerosis in patients with primary Sjögren's syndrome. *Clin Exp Rheum* 2016; 34: 1006-12.
  18. GUNTER S, ROBINSON C, NORTON G *et al.*: Cardiovascular risk factors and disease characteristics are consistently associated with arterial function in rheumatoid arthritis. *J Rheumatol* 2017; 44: 1125-33.
  19. CROWSON CS, ROLLEFSTAD S, IKDAHL E *et al.*: Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 2018; 77: 48-54.
  20. GIANNELLOU M, MAVRAGANI CP: Cardiovascular disease in systemic lupus erythematosus: A comprehensive update. *J Autoimmun* 2017; 82: 1-12.
  21. TSELIOS K, GLADMAN DD, SU J, ACE O, UROWITZ MB: Evolution of risk factors for atherosclerotic cardiovascular events in systemic lupus erythematosus: A longterm prospective study. *J Rheumatol* 2017; 44: 1841-9.
  22. BARTOLONI E, BALDINI C, SCHILLACI G *et al.*: Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. *J Intern Med* 2015; 278: 185-92.
  23. PEREZ-DE-LIS M, AKASBI M, SISO A *et al.*: Cardiovascular risk factors in primary Sjögren's syndrome: a case-control study in 624 patients. *Lupus* 2010; 19: 941-8.
  24. BARTOLONI E, ALUNNO A, GERLI R: Hypertension as a cardiovascular risk factor in autoimmune rheumatic diseases. *Nat Rev Cardiol* 2018; 15: 33-44.
  25. BARTOLONI E, ALUNNO A, VALENTINI V *et al.*: Role of inflammatory diseases in hypertension. *High Blood Press Cardiovasc Prev* 2017; 24: 353-61.
  26. AUGUSTO KL, BONFA E, RODRIGUES PEREIRA RM *et al.*: Metabolic syndrome in Sjögren's syndrome patients: a relevant concern for clinical monitoring. *Clin Rheumatol* 2016; 35: 639-47.
  27. WU XF, HUANG JH, CHIOU JY, CHEN HH, WEI J, DONG LL: Increased risk of coronary heart disease among patients with primary Sjögren's syndrome: a nationwide population-based cohort study. *Sci Rep* 2018; 8: 2209.
  28. ZARDI EM, SAMBATARO G, BASTA F, MARGIOTTA DP, AFELTRA AM: Subclinical carotid atherosclerosis in elderly patients with primary Sjögren's syndrome: a duplex doppler sonographic study. *Int J Immunopathol Pharmacol* 2014; 27: 645-51.
  29. ZARDI EM, BASTA F, AFELTRA A: Levels of Vitamin D, disease activity and subclinical atherosclerosis in post-menopausal women with Sjögren's syndrome: does a link exist? *In Vivo* 2016; 30: 721-726.
  30. RACHAPALLI SM, KIELY PD, BOURKE BE: Prevalence of abnormal ankle brachial index in patients with primary Sjögren's syndrome. *Clin Rheumatol* 2009; 28: 587-90.
  31. SABIO JM, SANCHEZ-BERNA I, MARTINEZ-BORDONADO J *et al.*: Prevalence of and factors associated with increased arterial stiffness in patients with primary Sjögren's syndrome. *Arthritis Care Res* 2015; 67: 554-62.
  32. CHIU M, AUSTIN PC, MANUEL DG, TU JV: Comparison of cardiovascular risk profiles among ethnic groups using population health surveys between 1996 and 2007. *CMAJ* 2010; 182: E301-310.
  33. CHEN C, SUNG KT, SHIH SC *et al.*: Age, gender and load-related influences on left ventricular geometric remodeling, systolic mid-wall function, and NT-ProBNP in asymptomatic Asian population. *PLoS One* 2016; 11: e0156467.
  34. DEMIRCI M, KARABULUT G, GUNGOR O, CELTIK A, OK E, KABASAKAL Y: Is there an increased arterial stiffness in patients with primary Sjögren's syndrome? *Intern Med* 2016; 55: 455-9.
  35. RAMOS-CASALS M, BRITO-ZERÓN P, SISÓ A *et al.*: High prevalence of eorum metabolic alterations in primary Sjögren's syndrome: influence on clinical and immunological expression. *J Rheumatol* 2007; 34: 754-61.
  36. ROBINSON CP, YAMACHIKA S, ALFORD CE *et al.*: Elevated levels of cysteine protease activity in saliva and salivary glands of the nonobese diabetic (NOD) mouse model for Sjögren syndrome. *Proc Natl Acad Sci USA* 1997; 94: 5767-71.
  37. BINDER A, MADDISON PJ, SKINNER P, KURTZ A, ISENBERG DA: Sjögren's syndrome: association with type-1 diabetes mellitus. *Br J Rheumatol* 1989; 28: 518-20.
  38. LODDE BM, SANKAR V, KOK MR, LEAKAN RA, TAK PP, PILLEMER SR: Serum lipid levels in Sjögren's syndrome. *Rheumatology* 2006; 45: 481-4.
  39. CRUZ W, FIALHO S, MORATO E *et al.*: Is there a link between inflammation and abnormal lipoprotein profile in Sjögren's syndrome? *Joint Bone Spine* 2010; 77: 229-31.
  40. IZUMI M, HIDA A, TAKAGI Y, KAWABE Y, EGUCHI K, NAKAMURA T: MR imaging of the salivary glands in sicca syndrome: comparison of lipid profiles and imaging in patients with hyperlipidemia and patients with Sjögren's syndrome. *Am J Roentgenol* 2000; 175: 829-34.
  41. KARABULUT G, KITAPCIOGLU G, INAL V *et al.*: Cigarette smoking in primary Sjögren's syndrome: positive association only with ANA positivity. *Mod Rheumatol* 2011; 21: 602-7.
  42. CROWSON CS, ROLLEFSTAD S, IKDAHL E *et al.*: Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 2018; 77: 48-54.
  43. BARTOLONI E, ALUNNO A, BISTONI O, GERLI R: Cardiovascular risk in rheumatoid arthritis and systemic autoimmune rheumatic disorders: a suggested model of preventive strategy. *Clin Rev Allergy Immunol* 2013; 44: 14-22.
  44. CANNARILE F, VALENTINI V, MIRABELLI G *et al.*: Cardiovascular disease in systemic sclerosis. *Ann Transl Med* 2015; 3: 8.
  45. KARAGEORGAS T, IOAKEIMIDIS D, MAVRAGANI CP: Psychological comorbidities associated with subclinical atherosclerosis in Greek patients with primary Sjögren's syndrome: a potential contribution of sleep impairment. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S68-72.
  46. ATZENI F, SARZI-PUTTINI P, SIGNORELLO MC *et al.*: New parameters for identifying subclinical atherosclerosis in patients with primary Sjögren's syndrome: a pilot study. *Clin Exp Rheumatol* 2014; 32: 361-8.