Psychological comorbidities associated with subclinical atherosclerosis in Greek patients with primary Sjögren's syndrome: a potential contribution of sleep impairment

T. Karageorgas[1,2], D. Ioakeimidis[3], C.P. Mavragani[1,4,5]

[1]Department of Physiology, School of Medicine, National and Kapodistrian University of Athens, Greece; [2]Rheumatology and Clinical Immunology Unit, 4th Department of Internal Medicine, University Hospital of Athens "Attikon", Greece; [3]Department of Rheumatology, General Hospital of Athens "G. Gennimatas", Greece; [4]Department of Pathophysiology, and [5]Joint Academic Rheumatology Program, National and Kapodistrian University of Athens, Greece.

Theofanis Karageorgas, MD, MSc
Dimitrios Ioakeimidis, MD
Clio P. Mavragani, MD, PhD

Please address correspondence and reprints request to:
Dr Theofanis Karageorgas, Rheumatology and Clinical Immunology Unit, 4th Department of Internal Medicine, University Hospital of Athens "Attikon", 1 Rimini Street, 12462 Athens (Attica), Greece.
E-mail: tkarageorgas@gmail.com

Received on December 8, 2016; accepted in revised form on February 6, 2017.

Clin Exp Rheumatol 2018; 36 (Suppl. 112): S68-S72.

Key words: Sjögren's syndrome, arteriosclerosis, sleep disorders

Funding: T. Karageorgas was supported by a State Scholarship Foundation (IKY) Fellowship of Excellence for Postgraduate Studies in Greece-Siemens Programme.

Competing interests: none declared.

ABSTRACT

Objective. *Impaired sleep and psychological disorders are increasingly recognised as prevalent comorbidities in patients with primary Sjögren's syndrome (pSS), as well as important contributors of atherosclerosis in the general population. In the current study we sought to explore a potential role of psychological comorbidities in the pronounced atherosclerotic risk of pSS patients.*

Methods. *Fifty-nine pSS patients fulfilling the ACR/EULAR criteria completed specific validated questionnaires assessing fatigue, depression, anxiety and sleep disturbances. Clinical, laboratory and histopathological characteristics together with traditional risk factors for atherosclerosis were documented in all enrolled patients. Subclinical atherosclerosis defined either as carotid and/or femoral plaque formation or increased intima media thickness (IMT) levels were assessed by Doppler ultrasound. Univariate and multivariate analysis were performed.*

Results. *Plaque formation and high IMT levels were detected by ultrasound in 41(69.5%) out of the 59 pSS patients. In univariate analysis, age and higher triglyceride serum levels were associated with both plaque formation and high IMT levels. Hypertension was associated only with high IMT levels. While increased rates of both state anxiety and impaired sleep were detected in pSS patients with plaque formation in a univariate model, only impaired sleep proved to be independently associated with plaque formation among pSS patients (OR=4.2, 95% CI=1.1–15.6, p=0.03).*

Conclusion. *This is the first study showing impaired sleep to confer a significantly higher risk of subclinical atherosclerosis in patients with pSS. Clinicians should take psychological disturbances into account when trying to assess and manage the cardiovascular disease risk of pSS patients.*

Introduction

Cardiovascular disease (CVD) is a well-established complication of systemic autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), severely affecting both the prognosis and mortality in these patients. Interestingly, increasing data recently reviewed by Valim *et al.* (1) suggest that cardiovascular risk is also heightened in primary Sjögren's syndrome (pSS). In fact, pSS is an independent risk factor for premature atherosclerosis (2) and exhibits a higher prevalence of myocardial infarction and cerebrovascular events compared to age-matched healthy women (3).

Various pathogenetic mechanisms have been evaluated involving both traditional and disease-associated risk factors for premature atherosclerosis. Despite certain studies based on large pSS registries (4) have shown an increased prevalence of traditional risk factors (*e.g.* hypertension, hypertriglyceridaemia, low HDL serum levels) the increased CVD risk cannot be entirely attributed to traditional factors for atherosclerosis. Moreover, pSS-related atherosclerosis has been associated with certain disease manifestations, such as leucopenia, anti-SSA/Ro positivity (5), Raynaud's phenomenon, central nervous system involvement (3), parotid enlargement, articular involvement, positive rheumatoid factor (6) as well as corticosteroid use.

Sleep disturbances, depression, anxiety and stress – already shown to be linked with CVD in both the general population and RA patients (9) – have been found to be highly prevalent in autoimmune populations including pSS (10). However, the impact of psychological burden in the atherosclerotic risk in the setting of

pSS is entirely unexplored. In the present study, we aimed to identify independent predictors of subclinical atherosclerosis in a cohort of pSS patients taking for the first time into account psychological and personality features.

Patients and methods

Study population

The present study, approved by the University of Athens Medical School Ethics Committee (approval no. 6337), enrolled 59 consecutive pSS patients who fulfilled the European American classification criteria (11) and were followed at the Rheumatology Outpatient Clinics of General Hospital of Athens "Laikon" and General Hospital of Athens "G. Gennimatas". In accordance with the Declaration of Helsinki, all patients provided informed consent prior to their entry in the study.

Clinical, serological and histopathological characteristics

Clinical, serological and histopathological characteristics were recorded after thorough chart review. These included the presence of arthralgias/myalgias, arthritis, fibromyalgia, myositis, subjective and objective measures of oral and ocular dryness, salivary gland enlargement, minor salivary gland biopsy, lymphadenopathy, vasculitis, Raynaud's phenomenon, lung, renal, liver involvement, peripheral and central nervous system involvement, lymphoma development. Moreover, laboratory data included anti-nuclear (ANA), anti-Ro/SSA, anti-La/SSB, anti-mitochondrial (AMA), anti-thyroid peroxidase and thyroglobulin (anti-TPO, anti-Tg), total γ-globulins, rheumatoid factor (RF), complement C3- and C4-levels, cryoglobulinaemia, serum electrophoresis, full blood count with differential, complete biochemistry panel, thyroid function tests and urinalysis. EULAR primary Sjögren's Syndrome Disease Activity Index (ESSDAI) was calculated as well as current and past medication history- including immunosuppressive and psychiatric medications- were documented.

Classical risk factors for atherosclerosis included the presence of family history of coronary disease (defined as a cardiovascular episode occurring below the age of 55 years in men and below 65 years in women in first degree relatives); past medical history of coronary heart disease, stroke, Diabetes Mellitus, hypertension; body mass index (BMI); smoking history; alcohol consumption (units/weeks) and total/current steroid use.

Psychometric scales

Psychological features were assessed using self-administered psychometric questionnaires: i) Zung Depression Scale, a validated tool for assessing depressive illness; ii) State-Trait Anxiety Inventory (STAI), a questionnaire used to assess anxiety either as a personality feature or as a current state; iii) Eysenck Personality Questionnaire (EPQ) Scale, a questionnaire that estimates temperamental aspects of behaviour based on the three independent axes of neuroticism, psychoticism and extraversion; iv) Athens Insomnia Scale (AIS), a questionnaire that assesses sleep disturbances and v) the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) scale was adopted in order to assess fatigue. The cut-off value for Zung Depression scale is >40, for State and Trait Anxiety Inventory >35, for the ERQ-Neuroticism>12, for the EPQ-Psychoticism >2, for the EPQ-Extroversion >9, for the AIS >6 and for FACIT-F <30 indicating severe fatigue. All questionnaires used have been validated for the Greek population and previously been implemented for psychiatric screening in autoimmune populations. Cut-off points were set according to the normative data derived from validation of scales in the Greek population.

Assessment of subclinical atherosclerosis

The presence of subclinical atherosclerosis was defined by the presence of plaque and/or arterial wall thickening (defined as intima media thickness (IMT) score >0.90 mm in carotid and femoral arteries as determined by ultrasound (iU22, Philips, Royal Philips Electronics of the Netherlands). Both the carotid (common carotid, bifurcation, and internal carotid) and the femoral (common femoral and superficial femoral) arteries were evaluated in each individual. The mean carotid artery IMT was defined as the average of 36 IMT readings (common, bifurcation, and internal carotid arteries, right and left side, far and near wall, with three sampling points per segment) and the mean femoral artery IMT was the average of twenty-four IMT readings common and superficial femoral arteries, right and left side, far and near wall, with three sampling points per segment), as previously described (5). Plaque formation was defined as a focal increase in thickness >50% of the surrounding vessel wall. The radiologist in charge of the ultrasound scanning was unaware of the clinical diagnosis of the subjects under evaluation.

Statistical analysis

Two-sided Fisher's exact/chi-square and Mann-Whitney tests were implemented to compare qualitative and quantitative characteristics, respectively, between patients with and without plaque. Univariate and multivariate analyses were performed in order to test whether the presence of plaque/IMT formation was independently associated with traditional risk factors for CVD and both disease-related and psychological/personality features. Multivariate models included determinants of atherosclerotic plaque that were found to be significant in univariate analysis. A p-value of <0.05 for univariate analyses and of <0.1 for multivariate analyses, respectively, were considered statistically significant. Data were stored in the SPSS statistical package.

Results

Associations between plaque formation and high IMT levels with traditional risk factors for CVD

Plaque formation and high IMT score were detected by ultrasound in 41(69.5%) out of the 59 pSS patients enrolled in this study. As shown in Table I, plaque formation (as well as high IMT levels) was associated with increased age (mean±SD = 62±10.75 *vs*. 53.8±15 years in patients with and without plaque respectively, p=0.048) and triglyceride levels (mean±SD = 117.1±48.9 *vs*. 83.9±21.8 mg/dL in patients with and without plaque re-

Table I. Traditional risk factors as predictors of plaque formation and high IMT levels in pSS patients.

Traditional risk factors	Plaque (n=41)	No plaque (n=18)	*p*-value	High IMT (n=41)	Normal IMT (n=18)	*p*-value
Age (yrs)	62 ± 10.8	53.8 ± 15	**0.048**	63 ± 10.3	51.3 ± 14.1	**0.022**
% of females	87.8	100	0.310	87.8	100	0.310
PMHx of CVD (%)	1 (2.4)	1 (5.6)	0.521	2 (4.9)	0 (0)	1.000
FHx of CVD (%)	5 (12.2)	1 (5.6)	0.656	4 (9.8)	2 (11.1)	1.000
Smoking (packs/year)	6.8 ± 16.9	3.8 ± 7.2	0.699	6.5 ± 17.1	4.3 ± 6.1	0.102
BMI	27.5 ± 5.4	25.9 ± 4.8	0.741	27.9 ± 5.2	25.2 ± 4.8	0.916
Diabetes (%)	5 (12.2)	0 (0)	0.310	3 (7.3)	2 (11.1)	0.636
Hypertension (%)	18 (43.9)	3 (16.7)	0.075	19 (46.3)	2 (11.1)	**0.016**
Cholesterol levels (mg/dL)	199 ± 32.5	190 ± 39.6	0.491	200 ± 33.5	190 ± 39.6	0.156
HDL(mg/dL)	57.7 ± 18.4	58.8 ± 15.6	0.596	59.7 ± 18.2	54.3 ± 15.6	0.945
LDL(mg/dL)	118.3 ± 30.5	120.8 ± 36.1	0.801	121.5 ± 34.5	113 ± 25.8	0.395
Triglycerides (mg/dL)	117.1 ± 48.9	83.9 ± 21.8	**0.006**	116.4 ± 48	85.4 ± 26.7	**0.002**
Lp(a)	21.0 ± 43.0	12.7 ± 8	0.454	22.6 ± 41.5	8.3 ± 8.8	0.559
Homocysteine levels (μmol/L)	14.7 ± 4.6	13 ± 3.8	0.372	14.5 ± 4.2	13.1 ± 4.6	0.700
CRP (mg/l)	3.2 ± 4.2	6.2 ± 10.8	0.941	4.5 ± 6.7	3.4 ± 7.5	0.636
Current steroid dose (mg/d)	2.4 ± 8.1	0.3 ± 1.2	0.147	2.3 ± 8.1	0.6 ± 1.6	0.296
Total steroid dose (g)	7.9 ± 16.6	1.7 ± 3.3	0.294	7.1 ± 16.3	3.6 ± 7.2	0.981

PMHx: past medical history; CVD: cardiovascular disease; FHx: family history; BMI: body mass index, HDL: high density lipoprotein; LDL: low density lipoprotein; CRP: C-reactive protein. Numerical values are expressed as mean±SD.

Table II. Disease-related features as predictors of plaque formation and high IMT levels in pSS patients.

Disease-related features	Plaque (n=41)	No plaque (n=18)	*p*-value	High IMT (n=41)	Normal IMT (n=18)	*p*-value
Disease duration (years)	11.4 ± 6.6	8.3 ± 4.6	0.117	10.2 ± 6.4	10.9 ± 5.9	0.57
SS Disease Activity Index	3.3 ± 2.6	3.2 ± 1.7	0.960	3.3 ± 2.5	3.17 ± 2.0	0.836
Focus score (no of foci/4mm^2)	3 ± 1.65	1.8 ± 0.8	0.287	3 ± 1.5	1.5 ± 0.7	0.462
Dry mouth (%)	40 (97.6)	17 (94.4)	0.521	40 (97.6)	17 (94.4)	0.521
Whole salivary flow (mL/15min)	1.9 ± 2.4	2.2 ± 1.9	0.426	1.9 ± 2.4	2.1 ± 1.9	0.637
Dry eyes (%)	38 (92.7)	17 (94.4)	1.000	37 (90.7)	18 (100)	0.303
ANA≥1/320 (%)	33 (80.5)	17 (94.4)	0.252	33 (80.5)	17 (94.4)	0.252
Anti-Ro/SSA (%)	30 (73.2)	13 (72.2)	1.000	28 (68.3)	15 (83.3)	0.343
Anti-La/SSB (%)	14 (34.1)	9 (50.0)	0.265	15 (36.6)	8 (44.4)	0.577
Rheumatoid factor > 20 IU/mL (%)	24 (58.5)	8 (44.4)	0.389	20 (48.8)	12 (67.7)	0.270
Low C4 (<16mg/mL) (%)	6 (14.6)	2 (11.1)	1.000	4 (9.8)	4 (22.2)	0.250
Absolute number of WBC (/mm^3)	6100 ± 2781	5482 ± 1563	0.873	6072 ± 2823	5543 ± 1406	0.499
Absolute number of lymphocytes (/mm^3)	1493 ± 763	1424 ± 425	0.316	1790 ± 1814	1425 ± 495	0.368
ESR (mm)	35 ± 24	32 ± 17	0.979	36 ± 22	28 ± 21	0.139
LDH (U/L)	206 ± 56.4	183.6 ± 28	0.160	202 ± 55	191 ± 35.7	0.860
β2 microglobulin (mg/dL)	2.6 ± 0.827	2.7 ± 0.875	0.782	2.8 ± 0.9	2.3 ± 0.83	0.246
Cryoglobulins (%)	0 (0)	0 (0)	1.000	3 (7.3)	0 (0)	0.546
Lymphoma (%)	8 (19.5)	1 (5.6)	0.252	7 (17.1)	2 (11.1)	0.708
Hydroxychloroquine use (%)	16 (39)	10 (55.6)	0.239	16 (39)	10 (55.6)	0.268

SS: Sjögren's syndrome; ANA: antinuclear antibodies; C: complement; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase. Numerical values are expressed as mean±SD.

spectively, p=0.006). Hypertension was significantly associated with high IMT levels (p=0.016) while showing a trend of association with plaque formation that however did not reach statistical significance (p=0.075).

Associations between plaque formation and high IMT levels with disease-related features

The results of the univariate analysis of disease-related features and plaque /IMT levels in this cohort of pSS patients are presented in Table II. None of the disease-related parameters was significantly associated with high IMT levels or plaque formation. Interestingly, albeit not statistically significant (p=0.239), more pSS patients without plaque and with normal IMT scores (55.6% for both) were treated with hydroxychloroquine compared to pSS patients with plaque and high IMT levels (39% for both) supporting the hypothesis of a possible protective role of hydroxychloroquine in atherosclerosis.

Associations between plaque formation and high IMT levels with psychological/personality features

The psychological and personality features included in this analysis were sleep disturbances, depression, anxiety (both state and trait), fatigue, fibromyalgia and personality traits, all previously reported to be strongly associated with

Table III. Psychological and personality-related features as predictors of plaque formation in pSS patients.

Psychological/personality-related features	Univariate analysis			Multivariate analysis*	
	Plaque (n=41)	No plaque (n=18)	*p*-value	OR (95%) CI	*p*-value
State Anxiety >35 (%)	34 (83)	10 (55.6)	**0.049**		
Trait Anxiety >35 (%)	31 (75.6)	15 (83.3)	0.735		
Depression >40 (%)	29 (72.5)	10 (55.6)	0.237		
Athens Insomnia Scale >6 (%)	27 (67.5)	6 (35.3)	**0.019**	**4.2** (1.1-15.6)	**0.03**
EPQ-P >2 (%)	16 (39)	8 (44.4)	0.777		
EPQ-N >12 (%)	28 (68.3)	9 (50)	0.244		
EPQ-E >9 (%)	29 (70.7)	11 (61.1)	0.550		
FACIT-F <30 (%)	11 (28.2)	5 (27.8)	1.000		
Fibromyalgia (%)	6 (15)	3 (16.7)	1.000		

*adjusted for age, triglyceride levels and state anxiety.
EPQ: Eysenck Personality Questionnaire: -P: psychoticism: -N: neuroticism; -E: extroversion; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue
Numerical values are expressed as mean±SD.

pSS. As displayed in Table III, both state anxiety and sleep disturbances were associated with plaque formation (83% *vs*. 55.6%, p=0.049 and 67.5% *vs*. 35.3%, p=0.019, respectively). Of note, in a multivariate model, impaired sleep assessed by AIS remained independently associated with plaque formation among pSS patients (OR = 4.2, 95% CI =1.1–15.6, p=0.03), after adjustment for all parameters shown to be significantly associated with plaque formation by univariate analyses (triglycerides serum levels, age, insomnia, state anxiety). An additional multivariate analysis was performed taking into account age, sex, smoking, BMI, blood pressure, cholesterol as well as current and total steroid dose and ESSDAI, which confirmed the independent association between sleep impairment and pSS-related atherosclerosis (OR = 1.1, 95%CI = 1.0–1.3). No association between IMT levels and psychometric variables were detected (data not shown).

Discussion

To our knowledge this is the first study in patients with pSS to explore the association of subclinical atherosclerosis with psychological, personality and sleep-related features of the patients beyond traditional and disease-related risk factors of atherosclerosis. Overall, two thirds of pSS patients in this cohort had evidence of subclinical atherosclerosis as assessed by ultrasound-detected high IMT levels and plaque formation. Interestingly, we found sleep disturbances to be independent predictors of plaque formation even after adjustment for traditional risk factors.

Most epidemiological studies in the general population concur that sleep impairment confers a small but sizeable risk of atherosclerosis even in the absence of obstructive sleep apnea (12). Several pathogenetic mechanisms have been implicated supporting the association of impaired sleep with atherosclerosis and CVD risk such as increased autonomic nervous system activity (*e.g*. nocturnal hypersecretion of norepinephrine, reduced heart rate variability), increased oxidative stress, altered inflammatory and coagulatory responses, as well as the association with obesity and unhealthy life-style (*e.g*. smoking) (13, 14).

Sleep disturbances are almost two-times more common in pSS patients than the general population (15) affecting approximately 50% of patients (10) partly due to sleep-perturbating sicca symptoms. To our knowledge this is the first study showing sleep disturbances to be strongly and independently associated with subclinical atherosclerosis in systemic autoimmune diseases even after adjustment for traditional risk factors as well as other psychological/personality features. Sleep impairment combined with other psychological (*e.g*. anxiety, depression) and somatic manifestations (*e.g*. fibromyalgia, fatigue) might lead to a sedentary life-style as well as to the activation of the aforementioned mechanisms thereby promoting premature atherosclerosis in these patients. However this hypothesis warrants further support from additional studies.

Hypertriglyceridaemia is a well-known risk factor of atherosclerosis and CVD risk. Hypertriglyceridaemia was also found to be significantly associated with atherosclerosis in two large cohorts of pSS patients (1) finding that was also replicated in our study. This is in keeping with the observation that in patients with chronic inflammatory conditions the two most commonly observed lipidaemic profile alterations are low high-density lipoproteins and high triglyceride serum levels. It has been suggested that, in this setting, hypertriglyceridaemia is due to both an increase in hepatic VLDL production and secretion and a decrease in the clearance of triglyceride rich lipoproteins. Of note, hydroxychloroquine has been shown to decrease the levels of triglycerides in patients with SLE and RA. Interestingly hydroxychloroquine use in our cohort was more common in patients without than with plaque formation and with normal than with high IMT levels (55.6% *vs*. 39% for both parameters); a finding that albeit not statistically significant, might partly be attributed to the beneficial effect of hydroxychloroquine in the lipidaemic profile of these patients. It should however be stressed out that hydroxychloroquine use did not influence the prevalence of atherosclerosis in a large UK pSS registry (4). Moreover, data from the same registry documented a higher prevalence of hypertension in pSS patients. Hypertension in our cohort was also significantly more prevalent among pSS patients with high IMT levels (p=0.016) and showed a trend of association with plaque formation which did not reach statistical significance (p=0.075) probably due to the smaller sample size of our study.

There are several limitations to our study. All patients were of Greek ethnicity therefore probably limiting the generalisability of our results in patients of different ethnic backgrounds. Additionally the modest number of patients with pSS enrolled in the study as well as the lack of a healthy control group warrant the confirmation of our

results in larger studies. However the strengths of this study derive from the concomitant analysis of a wide range of parameters associated with atherosclerosis including traditional risk factors, pSS-related clinical and serological activity indices as well as, for the first time, psychological and personality characteristics of the patients enrolled. Psychological, sleep-related and personality features of the patients participating in this study were assessed by the use of validated psychometric tools with stringent cut-offs.

In conclusion, for the first time sleep impairment was found to be an independent predictor of subclinical atherosclerosis in patients with pSS thereby highlighting the need for clinicians to assess and manage poor sleep quality and duration in their every-day care of these patients. Additionally higher triglyceride serum levels were also detected in this cohort of pSS patients and seem to confer a small but significant atherosclerotic risk in these patients. Clinicians should therefore include and treat (when appropriate) hypertriglyceridaemia in their regular CVD risk assessment of pSS patients. Taken together the findings from this and previous studies demonstrate that pSS-related atherosclerosis results from the complex interplay of traditional, disease-related and psychological/personality and sleep-related risk factors. Further studies are warranted in order to elucidate the exact contribution of each of these risk factors in pSS-related atherosclerosis.

Acknowledgements

Dr T. Karageorgas' work was supported by a State Scholarship Foundation (IKY) Fellowship of Excellence for Postgraduate Studies in Greece-Siemens Programme.

References

1. 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.
2. GRAVANI F, PAPADAKI I, ANTYPA E *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.
3. 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.
4. 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; 66: 757-64.
5. VAUDO G, BOCCI EB, SHOENFELD Y *et al*.: Precocious intima-media thickening in patients with primary Sjögren's syndrome. *Arthritis Rheum* 2005; 52: 3890-7.
6. GERLI R, VAUDO G, BOCCI EB *et al*.: Functional impairment of the arterial wall in primary Sjögren's syndrome: combined action of immunologic and inflammatory factors. *Arthritis Care Res* 2010; 62: 712-8.
7. FAN AZ, STRINE TW, JILES R, MOKDAD AH: Depression and anxiety associated with cardiovascular disease among persons aged 45 years and older in 38 states of the United States, 2006. *Prev Med* 2008; 46: 445-50.
8. NAKAZAKI C, NODA A, KOIKE Y, YAMADA S, MUROHARA T, OZAKI N: Association of insomnia and short sleep duration with atherosclerosis risk in the elderly. *Am J Hypertens* 2012; 25: 1149-55.
9. LIU YL, SZKLO M, DAVIDSON KW, BATHON JM, GILES JT: Differential association of psychosocial comorbidities with subclinical atherosclerosis in rheumatoid arthritis. *Arthritis Care Res* 2015; 67: 1335-44.
10. KARAGEORGAS T, FRAGIOUDAKI S, NEZOS A, KARAISKOS D, MOUTSOPOULOS HM, MAVRAGANI CP: Fatigue in primary Sjögren's syndrome: clinical, laboratory, psychometric, and biologic associations. *Arthritis Care Res* 2016; 68: 123-31.
11. VITALI C, BOMBARDIERI S, JONSSON R *et al*.: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
12. SCHWARTZ S, McDOWELL ANDERSON W, COLE SR, CORNONI-HUNTLEY J, HAYS JC, BLAZER D: Insomnia and heart disease: a review of epidemiologic studies. *J Psychosom Res* 1999; 47: 313-33.
13. TOBALDINI E, COSTANTINO G, SOLBIATI M *et al*.: Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases. Neurosci Biobehav Rev 2016;
14. MEZICK EJ, HALL M, MATTHEWS KA: Are sleep and depression independent or overlapping risk factors for cardiometabolic disease? *Sleep Med Rev* 2011; 15: 51-63.
15. SHEN C-C, YANG AC, KUO BI-T, TSAI S-J: Risk of psychiatric disorders following primary Sjögren syndrome: a nationwide population-based retrospective cohort study. *J Rheumatol* 2015; 42: 1203-8.