THU0161 SYNDECANS ARE CORRELATED WITH HIGH TITRES OF ANTIBODIES AGAINST CITRULLINATED PROTEINS ANTIGENS (ACPAs) IN SERA FROM ACTIVE RHEUMATOID ARTHRITIS

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Background: Syndecans includes a group of proteins from the cell-surface heparan-sulfate proteoglycan family, with a relevant role in chronic inflammation of synovial tissue in patients with rheumatoid arthritis (RA) participating in the cell-matrix and cell-cell interactions. Syndecans are differentially expressed in the synovial tissue: syndecan-1 (SDC-1) is expressed mainly in mononuclear cells, syndecan-3 (SDC-3) is mainly expressed by synovial endothelial cells and syndecan-4 (SDC-4) is expressed by B lymphocytes regulating B cell development and survival. Currently, there is strong evidence that antibodies directed to citrullinated protein antigens (ACPAs) are associated with a more severe disease in RA. Nevertheless, to date, there is a lack of information about the relation between serum syndecan levels and serum concentrations of rheumatoid factor (RF) and ACPAs.

Objectives: To evaluate the association between serum SDC-1, SDC-3 and SDC-4 levels with serum concentrations of RF and ACPAs.

Methods: Eighty-one, patients with RA were included. We assessed clinical characteristics including disease activity by DAS-28, functioning by HAQ-DI. Serum concentrations of RF were measured by nephelometry, two ACPAs were measured: anti-CCP2 and anti-mutated citrullinated vimentin (anti-MCV) antibodies using ELISA. Serum levels of SDC-1, SDC-3 (ng/mL) and SDC-4 (pg/mL) were measured by ELISA. We compared the serum levels of these syndecans in the ACPA+ group (group 1) versus ACPA- group (group 2) with Student t-test. A correlation analysis (Pearson tests) was performed to identify the strength of association between concentrations of syndecans with concentrations of ACPAs and other variables.

Results: Patients with RA had a mean age of 50±11 yrs, 75% were RF+ and 64% were ACPA+. In patients with ACPAs+ were observed higher serum concentrations of SDC-3 (p=0.003) and SDC-4 (p<0.001). SDC-1 correlated significantly with anti-MCV (r=0.53, p<0.001). Serum concentrations of SDC-3 correlated significantly with anti-CCP titres (r=0.53, p=0.003) and anti-MCV (r=0.46, p=0.02); whereas SDC-4 levels correlated significantly with anti-CCP titres (r=0.61, p<0.001) and RF (r=0.53, p=0.003). Additionally, serum SDC-1 levels correlated with decrement in response to treatment with synthetic DMARDs (r=-0.25, p=0.026). SDC-1 did not correlate with serum SDC-3 (p=0.8) and SDC-4 (p=0.8); whereas serum SDC-3 and SDC-4 had a strong correlation (r=0.8, p<0.001).

Conclusions: Serum SDC-3 and SDC-4 are increased in ACPA-positive RA patients. These data suggest that syndecans might be useful as serum biomarkers for discriminate a group of patients with RA and more severe disease.

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THU0162 RELATIONSHIP BETWEEN LEVELS OF HUMAN PEPTIDYL ARGININE DEIMINASE-4 WITH CHRONIC PERIODONTITIS SEVERE IN RHEUMATOID ARTHRITIS

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Background: Both Peptidyl arginine deiminase of *P. gingivalis* (pPAD), and the human enzyme (hPAD), could citrullinate peptides from the bacteria and human host in Rheumatoid Arthritis patients (RA). Chronic periodontitis (CP) could be associated with a constant generation of citrullinated proteins, and it lead to a proportional hPAD enzymatic production.

Objectives: The aim was to demonstrate the association between serum levels of hPAD4 and severe Periodontitis in patients with rheumatoid arthritis.

Methods: Patients with RA (n=127) matched with healthy controls (n=120) were

studied in a cross-sectional study. Levels of human recombinant antigens for hPAD4; cyclic citrullinated peptide antibody (CCP3, IgG), Rheumatoid factor (IgM) and C-reactive protein (CRP); determined by ELISA test.

The CP was classified according to the recommendations of the International Workshop for Classification of Periodontal Diseases and Conditions. Bivariate analysis to demonstrate the associations, and non-parametric analyzes were used according to the case.

Results: There were no significant demographic differences between the two groups. The median hPAD4 level was 1.21 (95% CI 1.4–1.7) in RA and 0.75 (95% CI 0.94–1.26) ng/ml in controls, (p<0.004). The median hPAD4 level in patients with RA and CP was 1.32 (95% CI 1.39–1.9) Vs control with CP 0.7 (95% CI 0.94–1.5) ng/ml, p<0.04.

The frequency of CP was higher in patients with RA than in controls (66.9 vs 43%, p<0.000; OR: 2.65 (95% CI: 1.58–4.44); these values showed a low correlation (0.24). The median level of hPAD4 was associated with CP extension, p<0.000 and severity, p<0.000.

A significant correlation was found between levels of hPAD4 with the DAS28 ESR score (p<0.002). The high score of HAQ-DI (>2.0) correlated with hPAD4 levels (P<0.001). The group of people with higher HAQ-DI score and at the same time with greater severity of CP (n=12) showed increased levels PAD4 (p<0.025).

Conclusions: hPAD4 levels correlate with the severity of CP independent of the RA presence and in RA subjects with high score of disability and activity disease. The hPAD4 could be proposed as a serological marker of clinical severity in chronic diseases such as CP and RA.

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THU0163 THE ASSOCIATION BETWEEN INFLAMMATORY JOINT DISORDERS AND CORONARY HEART DISEASE: NATIONWIDE REGISTER STUDY IN 50 444 PATIENTS

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Background: Inflammatory joint disorders (IJD) are associated with cardiovascular (CV) problems, including coronary heart disease (CHD). This association is best known for rheumatoid arthritis (RA); but also for ankylosing spondylitis and

Table 1. A) The prevalence of coronary heart disease (CHD) at the index date among patients with inflammatory joint diseases (IJD's) compared to their controls. B) The incidence of CHD among IJD patients compared to the controls during follow up.

		A) Index date*			B) Follow up*		
		CHD %		OR (95% CI)	Incidence of CHD per 1000 patient years		IRR
Men		Case	Control ^c		Case	Control	
RA+	6004	11.5	9.9	1.20 (1.09 to 1.33)	8.3	5.8	1.46 (1.27 to 1.67)
RA-	3071	10.3	9.2	1.14 (0.98 to 1.31)	6.1	5.4	1.12 (0.92 to 1.37)
UA	2503	5.9	5.8	1.03 (0.84 to 1.26)	5.8	3.8	1.51 (1.19 to 1.93)
SpA	4349	1.6	1.3	1.21 (0.90 to 1.64)	2.3	1.6	1.44 (1.09 to 1.89)
PsA	3424	3.9	3.9	1.04 (0.84 to 1.28)	4.5	3.3	1.36 (1.09 to 1.70)
Women							
RA+	12159	5.1	4.8	1.05 (0.95 to 1.16)	2.6	2.3	1.14 (0.98 to 1.32)
RA-	6713	5.7	4.7	1.26 (1.11 to 1.44)	2.6	2.0	1.32 (1.08 to 1.61)
UA	4896	3.0	2.7	1.11 (0.90 to 1.36)	2.5	1.5	1.67 (1.28 to 2.18)
SpA	4047	0.8	0.6	1.37 (0.89 to 2.11)	0.8	0.6	1.42 (0.87 to 2.31)
PsA	3278	2.0	1.6	1.23 (0.91 to 1.67)	2.2	1.5	1.53 (1.10 to 2.13)

* The date when the special reimbursement for IJD came effective

^b The time period after the index date until Dec 31st 2014

^c Three control subjects were matched for each patient with IJD

psoriatic arthritis (PsA). However, these findings are mainly based on materials from an era of less active treatment of the IJD's and thus progress in this theory may have happened. Further, many cases fail to fulfil any classification criteria. We found no published data on CV risk in unspecified arthritis (UA).

Objectives: To investigate the association between the five most common IJDs and CHD based on a nationwide large register data in Finland during 2000–14.

Methods: From the register maintained by the Social Insurance Institution (SII), we collected data on all Finnish patients granted a new special reimbursement (SR) on medications for the following IJDs during 2000–14: seropositive RA (ICD10 code M05), seronegative RA (M06), UA (M13), spondyloarthritis (SpA) (M45–46), and PsA (L40). For these patients, Population Register Centre matched three controls, standardized for age, sex, and place of residence. The index date was determined to be the date when the SR for IJD came effective. From the case and control groups we analysed the frequency of individuals that had SR also for CHD (ICD10 codes I20–25) at the index date, or to whom it was granted by SII during the observation period.

Results: Altogether 201 776 individuals (50 444 cases and 151 332 controls) were identified. The frequencies of the individuals having CHD by the index date and the incidences of CHD during follow-up are presented in table 1.

Conclusions: Compared to general population, CHD was overrepresented at RA diagnosis, especially in seropositive men and seronegative women, while other patients had comparable rates of CHD with the population. After the index day, the incidence of CHD was increased in all patient groups except for men with seronegative RA and women with seropositive RA or SpA. Thus, the CV risk associated to IJDs remains in this millennium, and also pertains to UA.

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THU0164 SUBCLINICAL ATHEROSCLEROSIS AND CARDIOVASCULAR EVENTS IN ITALIAN PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS FROM MULTICENTER GIRRCES (GRUPPO ITALIANO DI RICERCA IN REUMATOLOGIA CLINICA E SPERIMENTALE) STUDY

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Background: Several studies showed a close relationship between Rheumatoid Arthritis (RA) and accelerated atherosclerosis [1,2]. At the best of our knowledge, no such study has been carried out in a large Italian series.

Objectives: To investigate the prevalence of presence of subclinical atherosclerosis and history of cardio-cerebrovascular events (CVEs), in 1266 patients consecutively admitted to Rheumatology Units throughout the whole Italy.

Methods: From 01/01/2015 to 31/12/2015, 1266 consecutive patients admitted to GIRRCES centres, satisfying ACR/EULAR criteria for RA were investigated for: i. traditional cardiovascular risk factors: gender, age, smoking habit, cholesterol, triglycerides, glycemia, systemic arterial hypertension (SAH), metabolic syndrome (MS), type 2 diabetes (T2D); ii. RA aspects: disease duration as assessed from the first symptom, disease activity as evaluated by DAS28, radiographic damage by joint X-ray, and joint surgery; iii. subclinical atherosclerosis, as assessed by ultrasound technique and/or atherosclerotic peripheral lesions; iv. history of CVEs. **Results:** We evaluated 1176 patients out of 1266, that were investigated for both CVEs and subclinical atherosclerosis. They were mostly females (80.52%), with a median age of 60 years (range 18–91 years), a median disease duration of 12 years (range 0.8–25 years), seropositive in 69.21%. Nineteen percent were in remission; 17.51% presented low disease activity; 39.45% moderate disease activity, 22.61% high disease activity.

Out of 1176 patients, 217 (18%) showed evidence of subclinical atherosclerosis: a figure lower than that reported worldwide (32.7%) [2]. Eighty-two patients (6.9%) had a history for CVEs (58 myocardial infarction, 38 heart failure, 10 ischemic transitory attack, 7 Stroke), too this figure is lower than that reported worldwide (8.5%) [3,4]. In multivariate analysis, older age ($p=0.0001$, OR:1.069, CI95%:1.05–1.09), MS ($p=0.0001$, OR:3.417, CI95%:2.16–5.40) and SAH ($p=0.0001$, OR:3.714, CI95%:2.23–6.17) and high disease activity ($p=0.001$, OR:2.117, CI95%:1.35–3.32) were significantly associated with the presence of subclinical atherosclerosis. Male gender ($p=0.0001$, OR:3.465, CI95%:1.94–6.185), MS ($p=0.005$, OR:2.542, CI95%:1.29–4.52), T2D ($p=0.007$, OR:2.324, CI95%:1.29–4.29) and SAH ($p=0.001$, OR:4.921, CI95%:2.14–11.45) and higher disease activity ($p=0.003$, OR:1.316, CI95%:1.15–1.68) were significantly associated with a history of CVEs.

Conclusions: This is the first Italian multicenter study on subclinical and clinical

atherosclerosis in patients with RA. We pointed out a low prevalence of both subclinical atherosclerosis and history of CV events. Nonetheless, a high disease activity and presence of cardiovascular risk factors were found to play a role, similarly to other countries.

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THU0165 RISK OF HERPES ZOSTER IN PATIENTS WITH RHEUMATOID ARTHRITIS IN THE BIOLOGICS ERA BASED ON THE IORRA COHORT

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Background: A high incidence of herpes zoster (HZ) in patients with rheumatoid arthritis (RA) has been reported (1). According to our previous report on the incidence of HZ in Japanese patients with RA enrolled in the IORRA (Institute of Rheumatology, Rheumatoid Arthritis) cohort from 2005 to 2010, the standardized incidence rate (SIR) of HZ per 1,000 patient-years was 9.1 (95% confidence intervals [95% CIs]: 6.2–12.9) (2). In that study, 3.0% of patients used biologics at baseline. Subsequently, the use of biologics has increased, and many new potent disease-modifying antirheumatic drugs (DMARDs) have been introduced. The treatment strategy for RA has progressed in recent years; thus, it is important to investigate whether there is a change in the HZ incidence rate and the risk factors for HZ with the expanded use of biologics.

Objectives: To elucidate the incidence of HZ and risk factors for HZ in RA patients in the IORRA cohort.

Methods: The IORRA cohort is a large, single institute-based, observational cohort of RA patients established at the Institute of Rheumatology, Tokyo Women's Medical University, in 2000. Among patients with RA enrolled in the IORRA surveys from 2010 to 2015, the incidence of HZ was extracted based on patients' self-report and confirmed by the medical records. The SIR with 95% CIs was calculated and risk factors for HZ were analyzed using a Cox regression analysis.

Results: For 7,815 patients with RA (female, 84.7%) who were analyzed, the median [interquartile range (IQR)] age was 61.0 [49.7–68.9] years, and disease duration was 10 [4–18] years. Baseline drugs (median dose [IQR]) included prednisolone (PSL, 4 [2–5] mg/day) in 36.8%, methotrexate (MTX, 8 [6–10] mg/week) in 70.4%, and biologics in 14.7% of patients. Among 7,815 patients with 25,863 patient-years of observation (male, 3,828; female, 22,035), 340 HZ events were confirmed in 309 patients (21 patients had multiple events). The SIR per 1,000 patient-years was 8.5 (95% CI: 6.9–10.5) in total, 6.0 (95% CI: 3.7–9.2) in males, and 11.0 (95% CI: 8.7–13.7) in females. The following hazard ratios (HR) were found: unit increase of age, 1.14 (95% CI: 1.03–1.26, $p<0.05$); J-HAQ score 0.5–1.5 (reference J-HAQ score =0), 1.51 (95% CI: 1.09–2.10, $p<0.05$); MTX use, 1.58 (95% CI: 1.06–2.36, $p<0.05$); and biologics use, 1.88 (95% CI: 1.44–2.47, $p<0.01$). PSL use was not a risk factor (PSL dose <5 mg/day: HR 1.17 [95% CI: 0.91–1.51, $p=0.22$]; PSL dose $\geq$ 5 mg/day: HR 1.17 [95% CI: 0.72–1.91, $p=0.52$]; the reference PSL dose =0 mg/day).

Conclusions: The drugs that were a risk factor for HZ were PSL and MTX in our previous study when the use of biologics was not prevalent. In this study, the drugs that were a risk factor for HZ were MTX and biologics, but not PSL in the era when the use of biologics became frequent.

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