Objectives: Osteopontin (OPN) is required for osteoclast recruitment. We hypothesised that AD exacerbates bone erosion by inducing OPN expression in synovial tissue. This study aimed to evaluate a novel role for AD in RA.

Methods: The serum levels of AD and OPN were determined in 38 RA, 40 osteoarthritis (OA) patients, and 20 healthy controls using enzyme-linked immunosorbent assay (ELISA). AD and OPN production were measured by double immunofluorescence of RA and OA synovial tissue. Quantitative real-time PCR and immunofluorescence were used to evaluate the mRNA and protein expression levels of OPN in RA synovial fibroblasts (RASFs) and OA synovial fibroblasts after preincubation with AD, respectively. Migration of the RAW264.7 osteoclast precursors cell line was assessed using the Transwell migration assay and co-culture system. Bone destruction and osteoclastogenesis were assessed by immunohistochemistry, microcomputed tomography, and tartrate-resistant acid phosphatase (TRAP) staining in AD-treated collagen-induced arthritis (CIA) mice with or without OPN silencing. The expression levels of OPN and integrin $\alpha_v\beta_3$ in the ankle joint tissues of the mice were examined by double immunofluorescence.

Results: Our results indicated that the AD and OPN expression levels increased noticeably and were associated with each other in the RA serum. The AD distribution was coincident with that of OPN in the RA synovial tissue. AD stimulation of RASFs increased OPN production in a dose-dependent manner. AD-treated RASFs promoted RAW264.7 cell migration, and the effect was blocked with a specific antibody against OPN. Silencing of OPN using lentiviral-OPN short hairpin RNA reduced the number of TRAP-positive osteoclasts and the extent of bone erosion in the AD-treated CIA mice. When bound to integrin $\alpha_v\beta_3$, OPN functions as a mediator of AD and osteoclasts.

Conclusions: Our study provides new evidence of AD involvement in bone erosion. AD induces the expression of OPN, which recruits osteoclasts and initiates bone erosion. These data highlight AD as a novel target for RA treatment.

Disclosure of Interest: None declared

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THU0080 SERUM IRISIN AND MYOSTATIN LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) patients have loss of muscle mass. The balance between muscle protein synthesis and degradation is regulated by cytokines and growth factors, named myokines, such as irisin and myostatin. Myokines are mainly expressed by skeletal muscle and exert systemic effects promoting crosstalk among different tissues. Irisin increases cortical bone mass and its low levels are related to muscle atrophy and obesity^{1,2} while myostatin is a negative regulator of muscle growth and regeneration and has a direct role in osteoclastogenesis of inflammatory bone destruction^{3,4}.

Objectives: To evaluate serum levels of irisin and myostatin and body composition of RA patients and controls.

Methods: 122 female patients with RA, mean age 53 years, mean disease activity score (DAS28) 4.09, mean disease duration 11.2 years and mean body mass index 27.33 kg/m² were included. 69 age and sex-matched healthy subjects were enrolled as control group. Irisin (Phoenix Pharmaceuticals) and myostatin (R and D Systems) serum levels were evaluated by ELISA. Fat mass index (FMI;Kg/m²) and appendicular lean mass index (ALMI;Kg/m²) were assessed by total body dual-energy x-ray absorptiometry. Student's t test and Spearman correlation were performed. Significance was set at p<0.05.

Table 1. Irisin and myostatin serum levels of RA patients and controls

	n	Irisin (mean ±SD)	Myostatin (mean ±SD)
RA patients treated with biologics	13	31,71±7,69 [#]	2448,64±1114,90 [#]
RA patients non-treated with biologics	27	25,93±6,89	3261,66±1156,28 ⁺
Controls	30	30,36±10,95	4049,08±1610,01

[#]p<0,05 RA patients treated with biologics vs controls; ⁺p<0,05 RA patients treated with biologics vs RA patients non-treated with biologics; ⁺p<0,05 RA patients non-treated with biologics vs controls.

Results: RA patients had decreased serum levels of irisin (25,61±8,25 vs 30,36 ±10,95 ng/ml; p<0.05) and myostatin (3011,28±1271,11 vs 4049,08±1610,01 pg/

ml; p<0.05), decreased ALMI (6,09±0,88 vs 6,50±1,10; p<0.05) and increased FMI (11,26±3,30 vs 9,44±2,65; p<0.05), compared to controls. No correlations were observed among irisin and myostatin levels and ALMI and FMI. Of the 122 RA patients, 40 were analysed for the use of biologic medication. Serum levels of irisin and myostatin were different between RA patients treated and non-treated with biologics (table 1).

Conclusions: RA patients presented loss of lean mass and gain of fat mass, as well as lower irisin and myostatin serum levels, in comparison with controls. Additionally, the use of biologic medication by patients impacted on myokines serum levels. Further analyses are needed for a better comprehension of irisin and myostatin roles in RA, and to verify their correlation to other RA features.

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THU0081 IDENTIFICATION OF NOVEL AUTOANTIBODIES IN THE SYNOVIAL FLUID FROM PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a chronic, autoimmune and inflammatory joint disease with a poorly understood etiology. Despite widespread diagnostic use of anti-citrullinated protein antibodies and rheumatoid factor, there is strong demand for novel biomarkers to improve the diagnosis this disease.

Objectives: The purpose of present study is to investigate novel autoantibodies in the synovial fluid of RA patients.

Methods: 1) By using SEREX (Serological identification of antigens by recombinant cDNA expression cloning), we identified ten and several antigens from sera of RA patients. 2) Three epitope sites in the candidate antigens proteins were predicted and 18 mer peptides were synthesised. 3) Synovial fluid of the knees was obtained from 48 RA and 48 osteoarthritis (OA) patients. 4) Furthermore, Alpha-LISA was used to analyse the antibody levels in synovial fluid using synthetic polypeptide as antigens.

Results: Significantly higher proportion of antibodies against lamin A (LMNA, RA 19871+13924 VS OA 6726+3975, p<0.0000001) and cell growth-regulating nucleolar protein (CGRN, RA 19673+13314 VS OA 10614+6391, p<0.00007) were found in synovial fluid of RA as compared with OA.

Conclusions: We identified two novel autoantibodies in the knee synovial fluid of RA patients. These antibodies would have the potential to become diagnostic biomarkers of RA.

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THU0082 IMPAIRED LEFT VENTRICULAR RELAXATION AND ITS ASSOCIATION WITH INFLAMMATORY MARKERS IN COLLAGEN-INDUCED ARTHRITIS

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Background: Patients with rheumatoid arthritis (RA) experience an increased risk of developing heart failure with a preserved ejection fraction. Although there is some evidence to support a role of chronic inflammation in the pathogenesis of impaired left ventricular (LV) function in RA,¹ the direct effects of inflammatory cytokines on the LV function in collagen-induced arthritis (CIA) (an experimental model most similar to RA) require further elucidation.

Objectives: The aim of this study was to determine LV systolic and diastolic function and their association with circulating inflammatory markers in CIA.

Methods: Male Sprague Dawley rats were randomly divided into two groups: a control group (n=12) and a collagen-induced arthritis group (CIA, n=21). Rats in the CIA group were immunised with 0.2 ml type-II bovine collagen emulsified in incomplete Freund's adjuvant at the base of the tail followed by a 0.1 ml booster injection 7 days later. Eight weeks post-immunisation, markers of LV systolic function and geometry including ejection fraction (EF), fractional shortening (FS), stroke volume (SV) and LV end systolic diameter (ESD) were assessed echocardiographically using two-dimensional directed M-mode imaging. Markers of LV diastolic function including the early-to-late diastolic filling velocity ratio (E/A), the lateral (Lat e') and septal (Sep e') wall myocardial tissue lengthening at the mitral annulus and the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e') were assessed using pulsed Doppler and tissue Doppler echocardiography. Serum concentrations of interleukin 6 (IL-6), interleukin 1 β (IL-1 β), tumour necrosis factor alpha (TNF- α) and C-reactive protein (CRP) were determined by an enzyme-linked immunosorbent assay.

Results: No significant differences in markers of systolic function or geometry (EF, FS, SV and ESD) were observed between the groups ($p>0.05$). Compared to the control group, E/A (control=2.17 $\pm$ 0.39; CIA=1.46 $\pm$ 0.46; $p=0.0001$) and Sep e' (control=3.75 $\pm$ 0.69; CIA=3.23 $\pm$ 0.47; $p=0.04$) were lower in the CIA group. By contrast, E/e' (control=29.94 $\pm$ 6.99; CIA=24.17 $\pm$ 8.49; $p=0.13$) and Lat e' (control=3.99 $\pm$ 0.43; CIA=3.79 $\pm$ 0.78; $p=0.31$) did not differ amongst the two groups. IL-6 (115 $\pm$ 70.09 versus 365.3 $\pm$ 88.96 pg/mL; $p<0.0001$), IL-1 β (14.1 $\pm$ 55.7 versus 238.6 $\pm$ 49.01 pg/mL; $p<0.0001$), TNF- α (293.5 $\pm$ 87.16 versus 626.0 $\pm$ 119.7 pg/mL; $p<0.0001$) and CRP concentrations (0.23 $\pm$ 0.34 versus 0.97 $\pm$ 0.35 ng/mL; $p<0.0001$) were higher in the CIA compared to control group. A lower E/A was associated with TNF- α ($r=-0.63$; $p=0.0003$), IL-6 ($r=-0.56$; $p=0.0001$), IL-1 β ($r=-0.48$; $p=0.001$) and CRP concentrations ($r=-0.60$; $p=0.001$) in the total sample. Lower TNF- α ($r=-0.39$ $p=0.04$) and IL-1 β ($r=-0.47$, $p=0.01$) levels were associated with E/e' in the total sample.

Conclusions: Diastolic function is impaired in male Sprague Dawley rats with CIA. Our results indicate that exposure to high grade inflammation can reduce LV relaxation without impairing systolic function in CIA. Markers of inflammation were also associated with increased filling pressures in this animal model. Systemic inflammation may directly impact myocardial diastolic function in CIA.

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THU0083 CD30 APTAMER-SLAT-SHRNA CHIMAERAS INHIBIT TH17 DIFFERENTIATION BY ROR γ T IN RHEUMATOID ARTHRITIS

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Background: T helper 17 (Th17) cells play a central role in rheumatoid arthritis (RA) via the production of pro-inflammatory cytokines interleukin (IL)-17. SWAP-70-like adapter of T cells (SLAT) has recently emerged as an important regulator of Th17 differentiation. Aptamer-facilitated cell specific delivery of shRNA represents an attractive novel approach for efficient RNAi delivery. However, the role of CD30 aptamer-SLAT-shRNA chimaeras in regulating Th17 differentiation in patients with RA is unclear.

Objectives: SLAT play a crucial role in regulating Th17 cell differentiation and function. This study was undertaken to investigate the role and mechanism of SLAT in Th17 cells differentiation in patients with RA.

Methods: Peripheral blood CD4⁺ T cells and synovial fluid CD4⁺ T cells derived from RA patients and healthy controls were used to test the effect of SLAT *in vitro*. CD30 aptamer-SLAT-shRNA chimaeras were generated *in vitro* and transfected into CD4⁺ T cells. The effect of CD30 aptamer-SLAT-shRNA chimaeras on Th17 production and differentiation was detected.

Results: SLAT was expressed mostly in cytoplasm and cell membrane of CD4⁺ T cells. The protein levels of SLAT in peripheral blood and synovial fluid CD4⁺ T cells of RA patients were higher than that of healthy controls. The effect of CD30 aptamer-SLAT-shRNA chimaeras on Th17 differentiation was due to its ability to sequester SLAT and prevent it from targeting the transcription factor ROR γ T.

Abstract THU0083 – Figure 1. A. SLAT was expressed mostly in cytoplasm and cell membrane of CD4⁺ T cells. D. CD30 aptamer-SLAT-shRNA chimaeras reduced the percentage of CD4⁺ROR γ T⁺ cells and CD4⁺IL-17⁺ T cells.

Conclusions: This study reveals new evidence of the role of SLAT in Th17 differentiation in CD4⁺ T cells of RA patients.

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THU0084 HISTONE DEACETYLASE 1 (HDAC1): A NOVEL THERAPEUTIC TARGET IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Despite enormous efforts to develop new therapeutic strategies for treatment of rheumatoid arthritis (RA), the large number of non responding