Methods: Synovial tissue (ST) were sampled by Parker-Pearson needle biopsy from 67 RA patients who had completed one year follow-up from a prospective RA cohort [1]. ST from 13 patients with orthopedic arthropathies (Orth. A) with arthroplasty or arthroscopy were used as control. Expression of MUC1 in ST was assessed by immunohistochemistry (IHC). Radiographic assessments of hand/wrist at baseline and month 12 were performed with the Sharp/van der Heijde-modified sharp score. Radiographic joint damage (RJD) was defined as total modified Sharp score (mTSS) >10. Radiographic progression (RP) was defined as a change of mTSS more than 0.5 units.

Results: 1. Both nuclear and cytoplasmic MUC1 expression were observed in lining and sublining cells of synovium. The percentage of MUC1+ lining cells was significantly higher in RA (median 65.4%, IQR 53.6% 73.2%) than that in Orth. A (median 43.1%, IQR 3.4% 68.4%, $P < 0.05$).

2. Thirty-five (52%) RA patients showed RJD at baseline and their MUC1 expression in lining layer was significantly enhanced compared with RA patients without RJD (median 69.6%, IQR 64.5% 76.8% vs. median 58.9%, IQR 39.8% 67.9%, $P < 0.01$). Spearman's rank order correlation test showed significantly positive correlations between the percentage of MUC1+ lining cells with mTSS, joint space narrowing (JSN) subscore and joint erosion (JE) subscore at baseline ($r = 0.303-0.426$, all $P < 0.05$).

3. Furthermore, twenty-two (33%) patients suffered from one-year RP and they showed significantly positive percentage of MUC1+ lining cells than non-progressive patients (median 71.2%, IQR 55.2% 75.2% vs. median 64.1%, IQR 55.2% 75.2%, $r < 0.01$). The percentage of MUC1+ lining cells was positively correlated with mTSS, JSN and JE subscores at month 12 ($r = 0.310-0.405$, all $P < 0.05$). ROC curve analysis showed that the tradeoff value of MUC1+ lining cells for predicting one-year RP was 69% with sensitivity 72% and specificity 71% (AUC=0.661, 95% CI=0.516 0.805, $P=0.034$). Univariate logistic regression analysis showed that high MUC1+ lining cells was a significant predictor of one-year radiographic progression (OR: 5.893, 95%CI: 1.934 17.956, $P=0.002$).

Conclusion: Our data showed elevated MUC1 expression in RA synovial lining cells was positively correlated with joint damage and predicted one-year radiographic progression, which imply that MUC1 might be involved in the pathogenesis of RA joint destruction.

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Acknowledgement: This work was supported by National Natural Science Foundation of China (grant no. 81671612 and 81801605), Guangdong Natural Science Foundation (grant no. 2018A030313690 and 2017A030313576).

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.3884

THU0061

IN OVERWEIGHT SUBJECTS, SERUM ADIPONECTIN PREDICTS THE DEVELOPMENT OF RHEUMATOID ARTHRITIS INDEPENDENTLY OF OTHER ADIPOKINES

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Background: Adipokines, such as adiponectin, leptin, resistin and visfatin, are cytokines produced by the adipose tissue and involved in metabolism and inflammation¹. Adiponectin is elevated in both serum and synovial fluid of subjects with rheumatoid arthritis (RA), suggesting a possible role of this adipokine in the pathogenesis of RA^{2,3}. Circulating levels of leptin, resistin, and visfatin are also higher in subjects with RA compared to controls^{2,4}.

Objectives: Aim of this study was to determine if adiponectin, leptin, resistin, and visfatin predict the development of RA.

Methods: Two nested-case control studies were performed including pre-symptomatic participants of two cohorts from Sweden: the Swedish Obese Subjects (SOS) study and a cohort of individuals identified within the Medical Biobank of northern Sweden. The SOS is a clinical trial including 4047 subjects with obesity⁶. During a follow-up for up to 29 years, 92 subjects developed RA. Among those 92 subjects, 82 subjects with available serum at baseline were matched 1:5 with 410 subjects who did not develop RA during follow-up. Matching was based on baseline age, sex,

body-mass index (BMI), bariatric surgery yes/no, year of inclusion, and smoking. A nested case-control study of 88 sex- and age-matched pairs was performed within the Medical Biobank of Northern Sweden using blood samples donated before the onset of the first RA symptoms. The pre-dating time before onset of symptoms of RA was 8.5±5.0 years⁷.

Baseline serum levels of adiponectin, leptin, resistin, and visfatin were measured using the Quantikine ELISA kit from R&D Systems (Wiesbaden, Germany). Visfatin could not be measured in the Biobank cohort, due to lack of serum. Both binary logistic as well as conditional logistic regression analyses were used to determine if adipokines were elevated years before the onset of RA.

Results: In a multivariable analysis including adiponectin, leptin, resistin, visfatin performed in the SOS cohort, serum adiponectin was associated with a higher risk for RA independently of other adipokines (Odds ratio, OR, 1.1, 95% confidence interval, CI, 1.0-1.1, p value=0.01). Leptin, resistin and visfatin levels were not associated with the risk of RA.

In the Biobank cohort, no association between adipokines and risk for RA was detected. However, when stratifying the population according to BMI, in the subgroup having BMI>25 ($n=109$), adiponectin levels were associated with higher risk for RA (OR 1.2, 95% CI 1.0-1.36, $p=0.03$), independently of leptin and resistin levels. Virtually the same results were obtained in both the SOS and the Biobank cohorts when conditional logistic regression analysis was used.

Conclusion: Our results suggest that higher serum adiponectin levels predict the development of RA in subjects with overweight/obesity.

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Disclosure of Interests: Yuan Zhang: None declared, Linda Johansson: None declared, Anna Rudin Grant/research support from: I have received research grants från AstraZeneca (2017-2018), Consultant for: I was paid consultant for AstraZeneca (2015-2018), Lena Carlsson Consultant for: I have received lecture fees from AstraZeneca, MSD and Johnson&Johnson, Solbritt Rantapää Dahlqvist Consultant for: Member of the advisory board, Lipum AB, Umeå, Sweden., Cristina Maglio: None declared

DOI: 10.1136/annrheumdis-2019-eular.5314

THU0062

THE DYSREGULATION OF NK CELLS AND NON-CLASSICAL AND CLASSICAL MONOCYTE SUBPOPULATIONS IN INDIVIDUALS AT RISK OF DEVELOPING RHEUMATOID ARTHRITIS

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Background: Antibodies against citrullinated proteins (ACPA) are present months to years before the clinical manifestation of rheumatoid arthritis (RA). ACPA+ individuals are at 8-10x higher risk of developing RA compared to seronegative individuals. EULAR characterised individuals with arthralgia suspicious for progression to RA based on their clinical features (clinically suspect arthralgia, CSA).

Objectives: The alteration of natural killer (NK) cells and monocyte subpopulations in patients with established RA has been previously described. We therefore aimed to study the lymphocyte and monocyte subpopulations in individuals in the preclinical phase of RA.

Methods: Our study included 49 individuals with arthralgia (mean age 45.97±11.95 years; 92% females) and 80 age and gender matched healthy controls (HC). Leukocytes from peripheral blood were analysed by flow cytometry. Lymphocyte subpopulations were defined as B (CD19

+CD3-), T (CD3+CD4+, CD3+CD8+) and NK (CD16/56+CD3-) cells. Monocytes were further classified to classical (CD14++CD16-), intermediate (CD14++CD16+/+) and non-classical (CD14-/++CD16++) subsets. Data were analysed using Mann Whitney test and expressed as median and interquartile range [IQR].

Results: Out of 49 individuals with arthralgia, 36 were ACPA+ and 28 met CSA definition (15 of them were ACPA+), with symptoms duration 21 months [IQR=53], CRP 3.18 mg/L [IQR=3.6], DAS28 score 2.28 [IQR=1.31]. As per definition, there was no evidence of clinical arthritis on examination of 66 joints at baseline. Ten individuals developed RA within a median of 4 months of follow up.

Individuals with arthralgia had higher%CD3+ T cells (78.10 [8.10] vs. 75.04 [9.26], $p=0.001$) and lower%NK (11.20 [7.20] vs. 12.89 [6.62], $p<0.001$) as well as absolute count of NK cells (0.18 [0.13] vs. 0.24 [0.17], $p<0.001$) compared to HC. Similarly, higher%CD3+ T cells (77.95 [8.65] vs. 75.04 [9.26], $p=0.003$) and lower%NK (10.85 [7.81] vs. 12.89 [6.62], $p=0.003$) and absolute count of NK cells (0.20 [0.14] vs. 0.24 [0.17], $p=0.003$) was confirmed in a subgroup of ACPA+ individuals compared to HC. Moreover, individuals who developed RA during follow up, had a lower baseline absolute count of NK cells (0.14 [0.10] vs. 0.19 [0.15], $p=0.039$).

Analysis of monocyte subpopulations revealed higher count of non-classical (5.99 [4.87] vs. 4.03; IQR [3.28], $p=0.022$) and intermediate (5.82 [2.93] vs. 4.31 [2.08], $p=0.034$) monocytes and lower count of classical monocytes (86.06 [7.69] vs. 89.41 [3.52], $p=0.005$) in individuals with arthralgia compared to HC. Specifically, also ACPA+ patients had higher count of non-classical (6.07 [5.84] vs. 4.03 [3.28], $p=0.020$) and intermediate (5.86 [3.05] vs. 4.31 [2.08], $p=0.036$) and lower count of classical (85.43 [8.34] vs. 89.41 [3.59], $p=0.005$) monocytes compared to HC. There was no difference in% or absolute count of lymphocytes and monocytes subpopulations at the time of manifestation of RA and between ACPA+ and ACPA- individuals.

Conclusion: We show lower numbers of NK cells and classical monocytes and expansion of intermediate and non-classical monocytes in individuals in the preclinical phase of RA, especially in ACPA+ individuals. Such disproportion or pro-inflammatory potential of these cells was previously shown in the pathogenesis of established RA. We hypothesize that the dysregulation observed in at-risk individuals may be a prognostic marker and a predisposition leading to further development of RA.

Acknowledgement: Projects AZV-17-32612A and MHCR 023728

Disclosure of Interests: Klára Prajzlerová: None declared, Olga Kryštková: None declared, Petra Hánová: None declared, Hana Hulejová: None declared, Monika Gregová: None declared, Karel Pavelka: None declared, Jiří Vencovský Consultant for: Samsung, Speakers bureau: AbbVie, Novartis, Pfizer, Sanofi, Eli Lilly, Biogen, UCB, MSD, Werfen, Roche, Ladislav Šenolt Grant/research support from: AbbVie, Consultant for: AbbVie, Bristol-Myers Squibb, Celgene Corporation, Merck Sharp and Dohme, Novartis, Pfizer, Roche, UCB, Amgen, Takeda, Speakers bureau: AbbVie, Amgen, Bristol-Myers Squibb, Celgene Corporation, Eli Lilly, Merck Sharp and Dohme, Novartis, Pfizer, Roche, UCB, Mária Filková: None declared
DOI: 10.1136/annrheumdis-2019-eular.6686

THU0063

PRE-MRNA SPLICING ALTERATIONS IN FOLYLPOLYGLUTAMATE SYNTHETASE IN BLOOD CELLS OF EARLY RHEUMATOID ARTHRITIS PATIENTS ARE ASSOCIATED WITH UNRESPONSIVENESS TO METHOTREXATE

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Background: Low-dose methotrexate (MTX) serves as the first-line treatment for rheumatoid arthritis (RA). Conversely, for hematological malignancies, high-dose MTX treatment is indicated in combination with folinic acid/leucovorin to prevent untoward toxicity. For both disease modalities, efficient pharmacological response critically depends on the retention and accumulation of intracellular MTX. The latter process is mediated by the enzyme folylpolyglutamate synthetase (FPGS) through MTX conversion into MTX-polyglutamates (MTX-PG). As such, decreased FPGS activity has been recognized as a mode of MTX resistance, but the underlying molecular mechanism has not yet been pinpointed [1,2]. Recently,

aberrant pre-mRNA splicing of FPGS in acute lymphoblastic leukemia cells was associated with reduced FPGS activity, decreased MTX-PG accumulation and lower overall survival. Specifically, a partial retention of FPGS intron 8 (8PR) was identified as a prominent splice variant causing FPGS dysfunction [3].

Objectives: To investigate whether the expression of the FPGS pre-mRNA variant partial retention of intron 8 is associated with MTX unresponsiveness in RA patients over 3-6 months of MTX therapy.

Methods: Patients were enrolled from the COBRA-light trial comprising MTX treatment [4]. After informed consent, blood was obtained from 38 patients in either the COBRA (n=15) or the COBRA-light (n=21) treatment arm [4] and collected in Paxgene tubes for RNA isolation. Two patients were excluded due to insufficient sample quality. Quantitative PCR techniques were used to assess the ratios of FPGS 8PR over wild type FPGS (8WT) expression in whole blood RNA. Remission was defined as a DAS44 < 1.6.

Results: Baseline ratios of 8PR/8WT were associated with a decline in DAS44 at T3 ($p=0.001$) and T6 ($p=0.13$) in the COBRA-light patients. T3 ratios were also associated with DAS44 at T6 ($p=0.001$) and Δ DAS44 at T6 ($p=0.26$). Logistic regression analysis showed that in COBRA-light patients baseline ratios of 8PR/8WT were associated ($p=0.05$) with the probability of T3 remission but not T6 remission. T3 ratios of 8PR/8WT in COBRA-light patients were similarly associated with T6 remission but not with T3 remission. COBRA patients also showed a significant association between baseline 8PR/8WT ratios and DAS44 at T6 ($p=0.04$) while T3 ratios of 8WT/8PR were significantly associated with DAS44 at T3 ($p=0.03$) and T6 ($p=0.05$). However, analysis of COBRA patients showed no significant associations between baseline 8PR/8WT ratios and T3/T6 remission, nor associations between T3 ratios and T3/T6 remission.

Conclusion: These results demonstrate that a higher expression of an intron 8 retention of FPGS mRNA is associated with a higher DAS44 at T3 and T6 in COBRA-light patients, and at T6 for COBRA patients. Moreover, in COBRA-light patients, baseline expression of 8WT/8PR is significantly associated with remission at T3 or T6. This study is the first to show the impact of FPGS pre-mRNA splicing alterations in relation to unresponsiveness to MTX treatment in RA.

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Disclosure of Interests: Ittai Muller: None declared, Marry Lin: None declared, Willem Lems Speakers bureau: Amgen Inc., Merck, Eli Lilly and Pfizer, Marieke ter Wee Grant/research support from: Nonrestricted grant from Lilly Netherlands BV, Speakers bureau: ARC Preceptorship program, Jacqueline Cloos: None declared, Yehuda Assaraf: None declared, Gerrit Jansen: None declared, Robert De Jonge: None declared
DOI: 10.1136/annrheumdis-2019-eular.3215

THU0064

COMPARISON OF MORTALITY IN RHEUMATOID ARTHRITIS AND DIABETES – THE HUNT POPULATION-BASED STUDY

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Background: Patients with rheumatoid arthritis (RA) have higher mortality rates than the general population, primarily from cardiovascular disease (CVD). Diabetes is an acknowledged risk factor for early death, mainly due to CVD. The reported risk for CVD is increased for both patients with RA and diabetes, however the effect of diabetes appears to be greater than that of RA (1).

Objectives: To assess whether the increase in all-cause mortality rates in patients with RA and patients with diabetes are similar, compared to the general population.

Methods: Data were obtained from the 2nd and 3rd survey of the population-based Nord Trøndelag Health Study (HUNT) and the Norwegian National Cause of Death Registry. The RA diagnoses have previously been validated (2). The definition of diabetes was self-reported diabetes, self-reported use of antidiabetics, or non-fasting blood glucose level >11.1 mmol/L. The participants were followed from their participation in HUNT to death or to 31.12.2014, whichever came first. Participants with other types of inflammatory arthritis or missing data for any of the variables in