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Background: Clinical joint count assessment is important for detecting synovitis but its reliability is controversial

Objectives: This study assessed the correlation between bone scintigraphy and positron emission tomography (PET)-derived parameters in 28 joints with disease activity and compared the reliability of joint counts between bone scintigraphy and clinical assessment in rheumatoid arthritis (RA).

Methods: We enrolled 86 patients with active RA who underwent bone scintigraphy, fluorine-18-fluorodeoxyglucose (FDG) PET/CT and disease activity evaluation at the same time. This two-step study involved a development (n=67) and validation (n=19) group. Bone scintigraphy-derived joint assessment were compared with PET/CT derived and clinical joint assessment. Subsequently, we developed a disease activity score (DAS) using bone scintigraphy-positive joints and validated it in an independent group.

Results: The number of bone scintigraphy-positive joints in 28 joints was significantly correlated with the swollen (SJC)/ tender (TJC) joint counts and PET/CT derived joint counts. Intra- and inter-observer reliabilities of bone scintigraphy for the affected joint counts were excellent. Inter-observer reliability between nuclear medicine physicians and rheumatologists was good for SJC/TJC and PET/CT derived joint counts in 28 joints except shoulders. After multivariate analyses including erythrocyte sediment rate (ESR) and patients global assessment (PGA) in addition to bone scintigraphy-derived parameters, bone scintigraphy/DAS was derived as $0.056 \times \text{number of bone scintigraphy-positive joints in 28 joints} + 0.012 \times \text{ESR} + 0.030 \times \text{PGA}$. A significant correlation between bone scintigraphy/DAS and DAS28-ESR was confirmed in the validation group ($p < 0.001$).

Conclusion: Bone scintigraphy-derived joint assessment significantly correlated with PET/CT derived joint counts. Bone scintigraphy could serve as a sensitive and reliable method for evaluating disease activity in RA patients.

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THU0104

THE GUT MICROBIOTA AND ITS RELEVANCE TO PERIPHERAL T REGULATORY CELLS AND T HELPER 17 IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a common autoimmune disorder with joint destruction and synovial inflammation characterized by abnormal immune responses to autoantigens. Our previous studies have demonstrated that impaired peripheral lymphocytes especially insufficiency of regulatory T cells (Tregs) played an important role in pathogenesis of RA^{1,2}. Interestingly, the dysbiosis of gut microbiota triggers several types of autoimmune diseases through the imbalance of T lymphocyte subsets³. However, the detailed gut microbiota of RA patients and its correlation with Tregs and helper T cells 17 (Th17) are unclear up until now.

Objectives: To compare the difference of gut microbiota between RA and healthy controls (HCs), and to investigate the relevance of gut microbiota with circulating Tregs and Th17 in patients with RA.

Methods: From December 2018 to August 2019, a total of 205 diagnosed patients with RA and 199 age and sex-matched HCs were enrolled in this study. Stool of Every participant was collected for bacterial DNA extraction and 16S ribosomal RNA (rRNA) gene sequencing. The absolute numbers of Tregs and Th17 in PB of these individuals were measured by Flow Cytometer (FCM) combined with standard absolute counting beads. Data were expressed as mean $\pm$ standard deviation to the distribution. Independent-samples T test and Spearman rank correlation test. P value < 0.05 were considered statistically significant.

Results: Patients with RA had a significantly difference of diversity and abundance of intestinal microbiota compared with those of HCs ($P < 0.05$). Detailedly, the abundance of Proteobacteria was significantly increased in RA patients ($P < 0.05$), and the abundance of Firmicutes, Fusobacteria and Verrucomicrobia were significantly reduced ($P < 0.05$) at the level of Phylum (Figure 1). At the genus level, in the RA group, the abundance of Escherichia, Ruminococcus2 and Clostridium_sensu_stricto were significantly increased ($P < 0.05$), but the abundance of Lachnospiraceae_incertae_sedis, Prevotella, Clostridium_XIVa, Roseburia, Dialister, Blautia, Megamonas and Gemmiger were significantly lower than

the healthy controls ($P < 0.05$) (Figure 2). Moreover, Blautia, Anaerostipes and Ruminococcus2 have negative correlation with the absolute number of Tregs, and Cloacibacillus and Streptophyta have positive correlation with the absolute number of Th17.

Conclusion: Patients with RA had a dysbiosis of the gut microbiota in both diversity and abundance, which is closely related to the impaired peripheral lymphocyte subsets, that may be related to the pathogenesis of RA, which might provide a new idea for RA treatment.

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Figure1: The phylum-level profile for rheumatoid arthritis (RA) patients and healthy controls (HCs). Data were expressed as mean $\pm$ standard deviation to the distribution. Independent-samples T test was applied. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$)

Figure2: The genus-level profile for rheumatoid arthritis (RA) patients and healthy controls (HCs). Data were expressed as mean $\pm$ standard deviation to the distribution. Independent-samples T test was applied. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$)

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THU0105

ISOTOPE-LABELING-LC-MS-BASED METABOLIC PROFILING OF MULTIPLE SERUM SAMPLE SETS FOR THE DISCOVERY OF HIGH-CONFIDENCE RHEUMATOID ARTHRITIS BIOMARKERS

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Background: Early diagnosis of rheumatoid arthritis (RA) is hampered by sub-optimal accuracy of currently available serological biomarkers. Metabolomics may reveal promising biomarker candidates associated with the biomolecular processes of RA. In this work, we applied a high-performance chemical isotope labeling (CIL) LC-MS technique for in-depth profiling of the amine/phenol-submetabolome in serum samples. To avoid false positives and obtain high-confidence biomarker candidates, we analyzed three independent sets of serum samples collected from RA patients and healthy controls to examine the common effects.

Objectives: We aimed to identify a metabolite signature with consistently high accuracy for RA.

Methods: Serum samples were taken from 3 RA cohorts, which comprised 50, 49, and 131 RA patients, respectively. Within each cohort, there were

sex/age-matched healthy controls: 50 in Cohort 1, 50 in Cohort 2, and 100 in Cohort 3. Among these 446 subjects, 75% were females and the average age was 52.5 years. Amine/phenol-containing metabolites were labeled by ^{12}C -dansyl chloride to improve the LC-MS detection. For each cohort, a pooled sample was prepared and labeled by ^{13}C -dansyl group to serve as the reference sample for relative quantification. Then the individual samples and the pooled sample were mixed 1:1. Finally, an LC-QTOF-MS platform analyzed the mixtures and output the intensity ratios of $^{12}\text{C}/^{13}\text{C}$ peak pairs.

Results: 1,149 amine/phenol-containing metabolites were commonly detected across the three sample sets. Among them, 134 were positively identified by our dansyl-labeling standard library, and 141 were matched to predicted retention times and mass values of dansyl-labeled human metabolites. Visualized by the partial least squares discriminant analysis (PLS-DA), the overall amine/phenol-submetabolome demonstrated clear and consistent differences between healthy controls and the RA groups, with cross-validation $Q^2 = 0.765, 0.745, 0.793$, respectively. The selection of significant metabolites was conducted according to the fold change and false-discovery-rate-adjusted Welch's t-test. Cohort 1 demonstrated 85 metabolites having higher concentrations in the RA samples than the controls, and 89 metabolites with lowered concentrations. The numbers of increased/decreased metabolites in Cohort 2 and 3 were 87/26 and 90/53, respectively. Importantly, there were 59 significantly discriminatory metabolites commonly found in the three data sets (49 increased and 9 decreased). We picked the top three with the highest univariate classification performance to form a biomarker panel. We implemented the linear support vector machine (SVM) to build the classifier and the receiver operating characteristic (ROC) analysis to measure the performance. The area-under-the-curve (AUC) values (95% confidence interval) were 1.000 (1.000-1.000), 0.992 (0.967-1.000) and 0.902 (0.858-0.945) for the three cohorts, respectively. The results revealed the importance of examining multiple sample sets and even in the worst case (Cohort 3), our biomarker candidates could differentiate RA at 82.5% sensitivity and 82.5% specificity. Particularly, in Cohort 3, there were 30 RA patients negative for anti-cyclic citrullinated peptide and rheumatoid factor, and our metabolite panel demonstrated consistently high performance for differentiating these specific subjects from healthy controls.

Conclusion: Metabolites showing significant and consistent changes associated with RA have been identified with high discriminative power.

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THU0106

PREDICTORS OF FLARE IN RHEUMATOID ARTHRITIS PATIENTS WITH LOW DISEASE ACTIVITY

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Background: Low disease activity (LDA) in patients with rheumatoid arthritis (RA) are usually recognized as stable state. In according to most guidelines for RA, monotherapy of disease modifying anti-rheumatic drug (DMARD) was recommended for RA patients with LDA. But some of patients with LDA suffer from flare in their disease course. Until now, we don't have enough data on factors that can predict flare in RA patients with LDA.

Objectives: The aim of this study is to evaluate predictor of flare in RA patient with LDA from long-term (3 year) cohort data.

Methods: Korean observational study network for arthritis (KORONA) registry is a nationwide Korean RA specific cohort registry that collecting data annually from 5,376 RA patients in 23 centers across South Korea. We include the data from 1,801 RA patients with LDA (28 -joint disease activity score (DAS 28) < 3.2 at enrollment) who had consecutive data of DAS28 for 3 years. Flare was defined as an increase in DAS28 compared with baseline of >1.2 or >0.6 if concurrent DAS28 ≥3.2. Cox regression analysis was used to identify baseline predictors of flare.

Results: Among 1,801 RA patients, 673 patients (37.4%) experienced flare in 3 years. When we compare the baseline characteristics of both flare and non-flare group, more women and more non-adherent patients for medication were observed in flare group. Flare group had longer disease duration, lower EuroQol 5D score, higher health assessment questionnaire (HAQ) score, and higher

erythrocyte sedimentation rate (ESR) than non-flare group at baseline. In multivariate analysis, physician's VAS, HAQ score, ESR, and poor adherence for medication were significant predictors of flare (Table 1).

Table 1. Multivariate analysis of prediction of flare with baseline variables

Measure	Hazard ratio	95% Confidence Interval	P-value
Female	1.130	0.906-1.409	0.280
Age	0.996	0.988-1.005	0.414
Physician's VAS	1.008	1.002-1.013	<0.01
Pain VAS	1.002	0.998-1.006	0.34
EQ5D	0.952	0.534-1.696	0.87
HAQ	1.407	1.109-1.786	<0.01
ESR	1.008	1.002-1.014	<0.01
Poor adherence	1.272	1.047-1.545	<0.05

VAS: Visual Analogue Scale; EQ5D: EuroQol 5D; HAQ: Health Assessment Questionnaire; ESR: Erythrocyte Sedimentation Rate

Conclusion: RA patient who have risk factors for flare, even though their disease activity was low, require more proactive treatment.

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THU0107

OBSESITY PREDICTS RESPONSE TO NOT ALL BUT CERTAIN BIOLOGICAL / TARGETED DISEASE MODIFYING ANTI-RHEUMATIC DRUGS FOR RHEUMATOID ARTHRITIS - RESULTS FROM KANSAI CONSORTIUM FOR WELL-BEING OF RHEUMATIC DISEASE PATIENTS (ANSWER COHORT)

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Background: A number of previous reports suggested that obesity is one of the baseline factors indicates refractory to biologic disease-modifying antirheumatic drugs (bDMARDs). However, difference of the significant responses appears on obesity patients depending on each kind of drug is yet unclear. However, it is yet unclear how the significant responses on obesity patients vary on each kind of drug.

Objectives: To assess whether obesity affects clinical outcome in rheumatoid arthritis (RA) treated with each molecular-targeted agent including bDMARDs and tofacitinib.

Methods: In Kansai consortium for well-being of rheumatic disease patients (ANSWER) cohort, which was the real-world retrospective cohort of clinical database for rheumatic diseases, RA patients who initiated biological / targeted disease modifying anti-rheumatic drugs were included and consecutively followed. Obesity was defined as BMI over than 25, and patients were divided between