Background: Adiponectin is an adipokine that circulates in blood in three main forms, low molecular weight trimers, middle molecular weight hexamers, and high molecular weight (HMW) multimers [1]. It is still unclear which form of adiponectin is the predominant one to mediate the protein functions. Total adiponectin levels are elevated in both serum and synovial fluid of patients with rheumatoid arthritis (RA) [2], and total circulating adiponectin levels associate with inflammatory markers in a population at high risk for future RA [3]. However, the association of circulating adiponectin with markers of disease activity in subjects with RA is still matter of debate.

Objectives: The aim of the study was to determine whether total and/or HMW adiponectin levels associate with markers of disease activity and/or plasma chemokine levels in a cohort of subjects with untreated early RA.

Methods: The cohort consisted of 70 untreated subjects with newly diagnosed RA. Clinical disease activity markers, including DAS28, CDAI, CRP, and ESR, were assessed and data on patient history were recovered from clinical files. The plasma levels of 15 chemokines were measured with LED-ENDplex™ Human Proinflammatory Chemokine Panel or ELISA, and total and HMW adiponectin plasma levels were determined with ELISA. Multivariate factor analysis was used to examine the association between total and HMW adiponectin plasma levels with clinical disease activity markers and plasma chemokine levels. The multivariate models were used to select potentially associated markers and chemokines, which were then tested with linear regression.

Results: Both total and HMW adiponectin levels were associated with several clinical markers of disease activity (CRP, ESR, DAS28-ESR). Total adiponectin levels were also associated with DAS28-CRP. Furthermore, a positive association was found between total adiponectin levels and the pro-inflammatory chemokines CXCL10, CXCL9, and CCL2, whereas HMW adiponectin levels only associated with CXCL9.

Conclusion: This study shows for the first time that both total and HMW adiponectin levels are associated with several markers of disease activity as well as pro-inflammatory chemokines in a well-characterized cohort of subjects with untreated early RA. Those findings indicate adiponectin as a potential disease marker in subjects with RA.

Table 1. Clinical parameters

| Characteristic          | no=70 |
|-------------------------|-------|
| Women, no (%)           | 47 (69) |
| Age, yr                 | 51 (42-64) |
| BMI                     | 29 (23-28) |
| CRP, mg/L               | 9 (4-31) |
| ESR, mm/hour            | 18 (12-38) |
| SJC28                   | 9 (5-12) |
| TJC28                   | 9 (4-13) |
| DAS28-CRP               | 5 (4-6) |
| DAS28-ESR               | 5 (5-6) |
| ACFA+, no (%)           | 57 (81%) |
| RFI, no (%)             | 48 (69%) |
| CDAI                    | 28 (22-38) |
| Symptom Duration, months| 5 (3-8) |
| Smoking, no (%)         | 8 (11%) |

Data shown as median (interquartile range), unless otherwise noted.

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[1] Maeda N, Funahashi T, Matsuzawa Y, Shimomura I. Adiponectin, a unique adipocyte-derived factor beyond hormones. Atherosclerosis. 2019 Nov 2; 292:1-9.
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Results: Among the 1099 RA patients, 129 (11.7%) overlapped with SS validated by positive anti-SSA or pathological minor salivary gland biopsy (MSGB). After propensity score matching based on their baseline characteristics, 126 of 129 RA-SS and 126 of 970 RA-noSS patients were statistically extracted. Overlapping SS was associated with a 29%, 26%, 22% lower probability of reaching remission in RA patients based on DAS28-ESR, DAS28-CRP, SDAI, and CDAI, respectively, which trend kept true for reaching low disease activity (LDA) either. Although overlapping SS had the most significant impact on ESR (HR 0.69, 95% CI 0.61-0.79), other components assessing RA disease activity were also in jeopardy. When stratified by age, RA duration, and ACAP status, baseline DAS28-CRP, the trend remained.

Conclusion: Overlapping SS is associated with a lower probability of reaching target in RA patients, and should be regarded as one of the poor prognostic factors in the management of RA.

Table: Hazard Ratios for Reaching Remission/Low disease activity and Individual Components in RA patients Associated with Overlapping SS

| Remission Based on Composite Disease Activity Score | Unmatched cohort (n=1099) | Matched cohort (n=252) | Trimmed cohort (n=242) |
|---------------------------------------------------|--------------------------|------------------------|------------------------|
| DAS28-ESR                                         | 0.68 (0.62, 0.75)         | 0.71 (0.62, 0.82)      | 0.74 (0.64, 0.85)      |
| DAS28-CRP                                         | 0.80 (0.74, 0.87)         | 0.74 (0.66, 0.83)      | 0.74 (0.66, 0.83)      |
| SDAI                                              | 0.82 (0.74, 0.91)         | 0.82 (0.70, 0.94)      | 0.83 (0.72, 0.97)      |
| CDAI                                              | 0.77 (0.70, 0.86)         | 0.78 (0.67, 0.91)      | 0.78 (0.67, 0.91)      |
| Boolean                                           | 0.83 (0.75, 0.92)         | 0.80 (0.69, 0.93)      | 0.82 (0.70, 0.95)      |

| Remission/LDA Based on Composite Disease Activity Score | Unmatched cohort (n=1099) | Matched cohort (n=252) | Trimmed cohort (n=242) |
|--------------------------------------------------------|--------------------------|------------------------|------------------------|
| DAS28-ESR                                              | 0.76 (0.70, 0.82)         | 0.73 (0.65, 0.82)      | 0.74 (0.66, 0.83)      |
| DAS28-CRP                                              | 0.80 (0.74, 0.86)         | 0.76 (0.68, 0.84)      | 0.75 (0.68, 0.84)      |
| SDAI                                                   | 0.79 (0.73, 0.85)         | 0.74 (0.66, 0.82)      | 0.74 (0.66, 0.82)      |
| CDAI                                                   | 0.78 (0.73, 0.84)         | 0.74 (0.66, 0.82)      | 0.74 (0.66, 0.82)      |

| Individual Components of Disease Activity Score | Unmatched cohort (n=1099) | Matched cohort (n=252) | Trimmed cohort (n=242) |
|------------------------------------------------|--------------------------|------------------------|------------------------|
| 28SJ/C<sup>+</sup>                               | 0.83 (0.77, 0.89)         | 0.77 (0.69, 0.85)      | 0.76 (0.68, 0.84)      |
| 28TC/C<sup>+</sup>                                | 0.81 (0.75, 0.87)         | 0.79 (0.70, 0.84)      | 0.78 (0.70, 0.84)      |
| P<sub>G</sub>A<sub>A</sub>                        | 0.81 (0.74, 0.89)         | 0.82 (0.71, 0.94)      | 0.82 (0.72, 0.95)      |
| ESR<sub>ULN</sub>                                 | 0.66 (0.61, 0.73)         | 0.69 (0.61, 0.79)      | 0.70 (0.65, 0.84)      |
| CRP<sub>m</sub>g/dL                                | 0.84 (0.78, 0.90)         | 0.76 (0.68, 0.84)      | 0.77 (0.69, 0.85)      |

Table 1: Mediation Analysis for SE and ACAP Association with Change in DA

| Parameter | Change in DAS28 CRP (N=666) | Change in CDAI (N=653) | Change in SDAI (N=629) |
|-----------|-----------------------------|------------------------|------------------------|
| Total Effect of SE on DA change                  | 0.22 0.034 2.05 0.047 2.40 0.030 |                          |                        |
| Direct effect of SE on DA change excluding mediation of ACAP | 0.17 0.101 1.57 0.140 1.88 0.089 |                          |                        |
| Indirect effect of SE on DA change due to ACAP mediation and interaction | 0.04 0.183 0.48 0.133 0.51 0.143 |                          |                        |

Conclusion: SE is strongly related to ACAP and a greater burden of disease in RA pts. In pts receiving standard treatments including biologics, SE is predictive of a greater increase in DA, which is partially mediated by the presence of ACAP.

Disclosure of Interests: None declared

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[1] Dayan I, et al., Arch of Rheumatology, 2010;25:012-018.
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Figure 1. Linear Regression Model for SE association with Change in Disease Activity