

Baseline serum adipokine levels predict radiographic progression in early Rheumatoid Arthritis

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Introduction:

Adipose tissue can secrete different inflammatory cytokines and adipokines with potent regulatory factors, influencing whole body metabolism. Interestingly, obesity has been associated with a reduced radiographic progression in Rheumatoid Arthritis (RA). Adipose tissue can secrete soluble mediators (adipokines) with potent immune regulatory functions. Some adipokines have been previously associated with radiographic damage in Rheumatoid Arthritis (RA). In the present study we investigated the capacity of baseline adipokine levels to predict radiographic progression over a period of four years and studied their contribution relative to other known risk factors, such as anti-cyclic citrullinated peptide (anti-CCP) antibodies.

Table 1. Patient characteristics

Age mean (SD), years	56.1 (15)
Female, %	68.8
BMI mean (SD), Kg/m ²	25.6 (3.5)
non smoker, %	56.4
anti-CCP+, %	59
ESR, mm/hr	37 (22 - 59)
CRP, mg/L	20 (8 - 45)
Cytokines	
IL-6 (pg/ml)	28.9 (14.7 - 56.4)
TNFα (pg/ml)	5.4 (2.9 - 21.0)
Adipokines	
Resistin (ng/ml)	1.7 (1.1 - 2.4)
Visfatin (ng/ml)	10.0 (2.7 - 91.3)
Leptin (ng/ml)	12.9 (4.6 - 47.4)
Adipsin (μg/ml)	1.0 (0.8 - 1.7)
Adiponectin (μg/ml)	28.2 (15.6 - 47.5)
Total Sharp van der Heijde score (0 - 448)	
After 1 year	3 (0 - 8.8)
After 2 years	5 (1 - 15)
After 3 years	7 (2 - 19.8)
After 4 years	9.5 (3 - 27.3)

Unless indicated otherwise, medians (interquartile range) are depicted.
BMI = Body Mass Index; ESR = Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein.

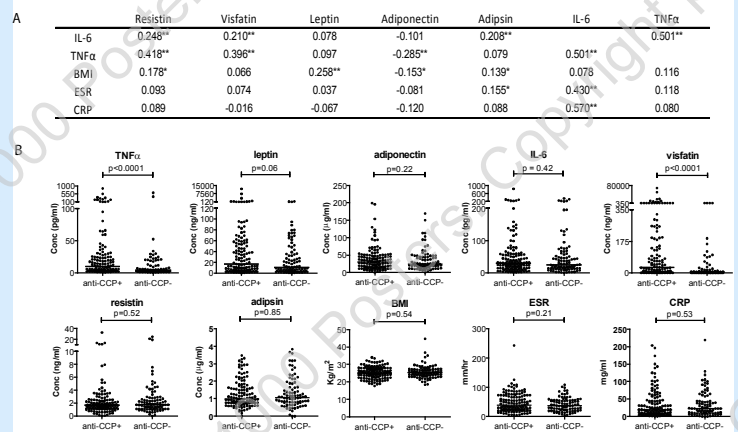


Fig.1 Spearman's Rank test correlation coefficients between adipokine levels, Body Mass Index (BMI) and inflammatory markers (A) and baseline differences in adipokine levels, BMI and acute phase reactants between anti-CCP+ and anti-CCP- patients (B) ESR = Erythrocyte Sedimentation Rate; CRP = C-reactive Protein. *P<0.05; **P≤0.001 by Spearman's Rank test

Table 2. Predictive capacity

	estimate	Lower bound	Upper bound	Sig.
Model 1 (Basic)				
TNFα	1.09	1.04	1.14	<0.001*
IL-6	1.10	1.03	1.16	0.003*
visfatin	1.03	1.01	1.05	<0.001*
resistin	0.95	0.88	1.02	0.126
leptin	1.04	1.00	1.08	0.046
adipsin	3.98	0.01	1000	0.669
adiponectin	1.28	1.10	1.49	0.002*
Model 2 (Basic + BMI)				
TNFα	1.09	1.04	1.14	<0.001*
IL-6	1.10	1.03	1.16	0.003*
visfatin	1.03	1.02	1.05	<0.001*
adiponectin	1.26	1.09	1.47	0.003*
Model 3 (Basic + anti-CCP)				
TNFα	1.04	0.99	1.10	0.123
IL-6	1.08	1.01	1.15	0.019
visfatin	1.01	0.99	1.03	0.129
adiponectin	1.24	1.06	1.45	0.008*
Model 4 (Basic + BMI and anti-CCP)				
TNFα	1.05	0.99	1.10	0.100
IL-6	1.08	1.01	1.15	0.021
visfatin	1.02	1.00	1.04	0.098
adiponectin	1.22	1.05	1.44	0.012*

Repeated Measurement Analysis (RMA) with Sharp van der Heijde (SvdH) scores over 4 years, as outcome. The indicated adipokines were modeled individually and analyses were corrected for age, gender, treatment strategy (Basic model) and as indicated, for Body Mass Index (BMI), anti-cyclic citrullinated peptides (anti-CCP) or both.

Estimates are calculated as described in "Patients and Methods". Bonferroni's correction was used to determine significance. *A P-value ≤ 0.007 (Model 1) or ≤ 0.013 (Model 2-4) was considered significant.

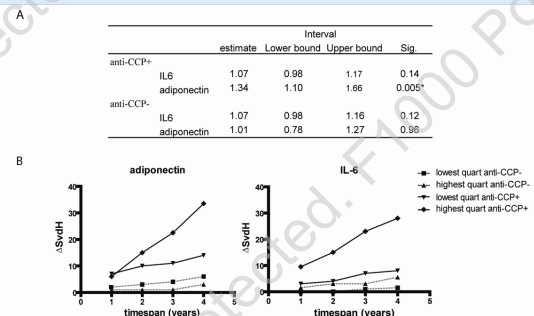


Fig. 2. Repeated Measurement Analysis (RMA) with Sharp van der Heijde (SvdH) scores over 4 years as dependent variable, in anti-CCP+ and anti-CCP- patients. (A) Analyses were corrected for age, gender, treatment strategy and Body Mass Index. Estimates were calculated as described in "Patients and Methods" section. Significance was calculated using Bonferroni's correction. *A P value ≤ 0.025 was considered significant. Adipokine concentrations are expressed in pg/ml for IL-6 and μg/ml for adiponectin. (B) Median rates of joint destruction (ΔSvdH scores over indicated timespans) are depicted for lowest and highest quartiles of adipokines in anti-CCP+ (black lines) and anti-CCP- patients (dotted lines).

Results and Discussion:

IL-6, TNFα, visfatin and adiponectin levels associated positively with radiographic progression over four years. This association was independent of BMI. However, only adiponectin levels remained significantly associated with progression when corrected for the presence of anti-CCP antibodies, whereas a trend was observed for IL-6. The association of both TNFα and visfatin with radiographic damage seemed dependent on anti-CCP antibodies, which is in line with the fact that the levels of both cytokines correlated significantly with anti-CCP levels in these patients. Stratification for the presence of anti-CCP antibodies revealed that adiponectin associated with progression only in anti-CCP+ disease.

Our results indicate that adipokines are predictors for radiographic progression in RA, possibly through distinct underlying biological mechanisms.