Are Baseline High Molecular Weight Adiponectin Levels Associated with Radiographic Progression in Rheumatoid Arthritis and Osteoarthritis?

Inge R. Klein-Wieringa, Stefan N. Andersen, Linda Herb-van Toorn, Joanneke C. Kwekkeboom, Anette H.M. van der Helm-van Mil, Ingrid Meulenbelt, Tom W.J. Huizinga, Margreet Kloppenburg, René E.M. Toes and Andreea Ioan-Facsinay

J Rheumatol 2014;41;853-857
http://www.jrheum.org/content/41/5/853

1. Sign up for our monthly e-table of contents
http://www.jrheum.org/cgi/alerts/etoc

2. Information on Subscriptions
http://jrheum.com/subscribe.html

3. Have us contact your library about access options
Refer_your_library@jrheum.com

4. Information on permissions/orders of reprints
http://jrheum.com/reprints.html

The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Are Baseline High Molecular Weight Adiponectin Levels Associated with Radiographic Progression in Rheumatoid Arthritis and Osteoarthritis?

Inge R. Klein-Wieringa, Stefan N. Andersen, Linda Herb-van Toorn, Joanneke C. Kwekkeboom, Anette H.M. van der Helm-van Mil, Ingrid Meulenbelt, Tom W.J. Huizinga, Margreet Kloppenburg, René E.M. Toes, and Andreea Ioan-Facsinay

ABSTRACT. Objective. To investigate whether high molecular weight adiponectin (hmwAPN) mediates the associations of total adiponectin (totAPN) with radiographic progression in rheumatoid arthritis (RA) and hand osteoarthritis (HOA).

Methods. Associations between baseline hmwAPN or totAPN levels with radiographic progression were determined using multivariate linear regression or generalized estimated equations.

Results. In patients with RA, totAPN associated positively, whereas in patients with HOA it associated negatively with radiographic progression. In contrast, hmwAPN did not associate significantly with radiographic progression in either cohort.

Conclusion. Our data indicate that the differential effects associated between totAPN and radiographic progression in either RA or HOA are not mediated by hmwAPN. (First Release April 1 2014; J Rheumatol 2014;41:853–7; doi:10.3899/jrheum.130888)

Key Indexing Terms:
RADIOGRAPHIC PROGRESSION TOTAL ADIPONECTIN HAND OSTEOARTHRITIS HIGH MOLECULAR WEIGHT ADIPONECTIN RHEUMATOID ARTHRITIS

Obesity has been associated with altered radiographic progression in rheumatoid arthritis (RA) and hand osteoarthritis (HOA)1,2. While the underlying mechanisms of these associations remain unclear, it is believed that adipose tissue secreted factors (adipokines) could play an important role in systemic effects of obesity. Therefore, several studies have investigated the association of adipokines with disease progression in RA and OA. Some adipokines, including adiponectin, have been shown to influence joint damage. In patients with RA, total adiponectin (totAPN) levels in serum associated positively with radiographic progression, suggesting a predisposing effect on disease3. Intriguingly, high totAPN levels in the serum of patients with HOA were associated with reduced relative risk for disease progression1, indicating a protective effect.

Adiponectin is a pleiotropic adipokine that consists of several isoforms in circulation: a trimeric low molecular weight adiponectin; a hexameric middle molecular weight adiponectin, and a multimeric high molecular weight adiponectin (hmwAPN). In addition, although its presence in serum has been questioned, a globular form of adiponectin exists, resulting from proteolytic cleavage of totAPN4. Of the different adiponectin isoforms described, hmwAPN emerges as one of the most biologically active isoforms in circulation5. Although both proinflammatory and antiinflammatory actions have been attributed to this isoform, its role in disease progression in RA and in HOA remains unknown6,7. Here, we explored the possibility that the association of totAPN with disease progression in RA and HOA is primarily mediated by hmwAPN, indicating that the association of totAPN with radiographic progression could be dependent on hmwAPN.

MATERIALS AND METHODS
Patients selected from the Leiden Early Arthritis Cohort (EAC) and the Genetics, ARthrosis and Progression (GARP) study were included in our study8,9. Both studies were approved by the Medical Ethical Committee of the Leiden University Medical Center. The 324 patients with RA selected from the EAC fulfilled the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA within the first year of followup (n = 324) and presented to the Leiden EAC between 1993 and 20023. This study included 324 patients in total, whereas previously supported by TI-Pharma, EU FP6 program Autocure, FP7 program Masterswitch, a grant from Centre for Medical Systems Biology within the framework of the Netherlands Genomics Initiative, and the Netherlands.

I.R. Klein-Wieringa, MD; S.N. Andersen, Analyst; L. Herb-van Toorn, Analyst; J.C. Kwekkeboom, Analyst; A.H.M. van der Helm-van Mil, MD, PhD, Head of the Outpatient Clinic, Department of Rheumatology, Leiden University Medical Center; I. Meulenbelt, PhD, Associate Professor, Department of Molecular Epidemiology, Leiden; T.W.J. Huizinga, MD, PhD, Professor; M. Kloppenburg, MD, PhD, Professor; R.E.M. Toes, PhD, Professor; A. Ioan-Facsinay, PhD, Assistant Professor.

Address correspondence to Dr. A. Ioan-Facsinay, Dept. of Rheumatology, C1-R, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: A.ioan@lumc.nl

Accepted for publication January 31, 2014.
samples of 253 patients were tested. Because of limited availability of serum, plasma was used in our study. Yearly obtained radiographs of hands and feet were scored according to the Sharp/van der Heijde method by 1 experienced scorer (MvdL) who was blinded for each patient’s autoantibody status, treatment, and clinical outcome. The intrareader variability described by the intraclass correlation coefficient (ICC) was 0.97 for the radiographic progression rate. As described, treatment strategy was considered a possible confounder and was corrected for in subsequent analyses.

Of the 384 total patients included in the GARP study, 344 fulfilled the ACR criteria for clinical HOA, or had a Kellgren-Lawrence score ≥ 2 in ≥ 1 hand joint. Radiographs of the hands were available at baseline and after a mean of 6.1 years for 227 of these patients. This study included 227 patients in total, whereas previously samples from 164 patients were tested. Thirty-two hand joints were scored for joint space narrowing (JSN) by a team of 2 experienced scorers (IWH/JB) who were blinded for patient characteristics as described. The intrareader variability was good (ICC 0.87). Progression was defined as the difference between the sum of JSN scores at followup and at baseline that was above the smallest detectable change of 1.5.

Laboratory assessments. Baseline plasma (RA) and serum (OA) samples were stored at −80°C. Concentrations of total adiponectin (μg/ml) were measured using the Bio-Plex Pro Human Diabetes kit (Bio-Rad, range 33–500,000 pg/ml), the Bio-Plex array reader, and Bio-Plex software, following the manufacturers’ instructions. Concentrations of hmwAPN (μg/ml) were measured by ELISA (Merck Millipore, range 3.125–200 ng/ml), according to the manufacturer’s instructions. Differences in levels of total and hmwAPN could be due to different experimental techniques used to quantify them.

Statistical analyses. Body mass index (BMI) was normally distributed in the study populations. Correlations between BMI and adiponectin levels were calculated using Spearman’s rank correlation test. A correlation coefficient (r) below 0.2 was considered very weak; between 0.2 and 0.4 as weak; between 0.4 and 0.7 as moderate, and above 0.7 as strong.

We investigated whether circulating levels of hmwAPN correlated with HOA progression, while confirming that total adiponectin levels are. hmwAPN, however, was not associated with progression, nor did levels differ between progressive and nonprogressive patients (Figures 3A and 3C).

DISCUSSION

We investigated whether circulating levels of hmwAPN could mediate the association of total adiponectin with disease progression in RA and HOA. We have shown that hmwAPN is not significantly associated with radiographic progression, while confirming that total adiponectin levels are. hmwAPN, therefore, does not appear to be the main contributing isoform to the associations of total adiponectin with radiographic progression in RA and HOA.

The association between total adiponectin in serum and progression has been reported. In our present study we showed a similar association with plasma total adiponectin levels. Notably, total adiponectin levels in plasma were lower than in serum when paired samples were tested (data not shown).

To our knowledge, this is the first study investigating the association of circulating hmwAPN levels with disease progression in RA. The proinflammatory and antiinflam-
Figure 1. A. Patient characteristics of the Early Arthritis Cohort (EAC) and the Genetics ARthrosis and Progression (GARP) cohort. Spearman’s rank test correlation coefficients between total adiponectin (totAPN) and high molecular weight adiponectin (hmwAPN) in plasma of EAC (B) and serum of GARP (C) patients. Unless otherwise specified, values depicted are medians (interquartile range). A p value < 0.05 was considered significant. BMI: body mass index; RA: rheumatoid arthritis; anti-CCP: anticyclic citrullinated peptide; SvdH: Sharp/van der Heijde scores; OA: osteoarthritis.
matory effects of hmwAPN are still being debated\textsuperscript{12,13} and could depend on the disease studied and the experimental setting. However, our results are in line with a study that indicated that all isoforms can exert potent proinflammatory effects on RA synovial fibroblasts and monocytes \textit{in vitro}\textsuperscript{6,14}. Although there was a trend toward an association between hmwAPN and progression of RA, the size of this association is considerably less than for totAPN, indicating a possible contribution of other isoforms to the observed association, or a possible modulatory effect of local environmental factors, which could result in a stronger local effect\textsuperscript{6,14} than systemic effects of hmwAPN.

The inverse association of adiponectin with radiographic progression in HOA is intriguing, because the different forms of adiponectin have proinflammatory effects on OA synoviocytes, and circulating adiponectin levels are associated with synovial inflammation in knee OA\textsuperscript{14,15}. In addition, higher levels of adiponectin have previously been suggested in patients with erosive compared to nonerosive HOA\textsuperscript{16}. These differences may lie in differences in study cohort or differences in determination of radiographic damage.

Because synovial inflammation has been associated with radiographic progression in knee OA\textsuperscript{17}, these data suggest a deleterious effect of adiponectin on disease progression rather than a protective effect. This could be caused by a different effect of synovial inflammation on radiographic progression in HOA compared to the knee or by a different effect of adiponectin on synoviocytes of the hand joint compared to the knee joint. The mechanisms underlying this discrepancy remain to be further investigated.

While our data await replication, there was a clear inverse association between totAPN and HOA progression and this association was not observed for hmwAPN, indicating that other isoforms could mediate the observed association.

Our study further substantiates the known associations of totAPN with radiographic progression in RA and HOA and indicates that these associations are not mediated by a selective effect of hmwAPN.

**ACKNOWLEDGMENT**

We are indebted to Dr. M. van der Linden, Prof. Dr. I. Watt, and Dr. J. Bijsterbosch for scoring the radiographs.

**REFERENCES**


<table>
<thead>
<tr>
<th></th>
<th>non-progressive (n = 165)</th>
<th>progressive (n = 62)</th>
<th>Odds ratio (95% Confidence Interval)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>basic model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TotAPN (9 missing)</td>
<td>&lt;17.6</td>
<td>42</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.6 - 28.8</td>
<td>59</td>
<td>14</td>
<td>0.36 (0.16 - 0.78)</td>
</tr>
<tr>
<td></td>
<td>&gt;28.8</td>
<td>59</td>
<td>14</td>
<td>0.31 (0.13 - 0.70)</td>
</tr>
<tr>
<td>HmwAPN (23 missing)</td>
<td>&lt;2.2</td>
<td>51</td>
<td>17</td>
<td>1 (reference)</td>
</tr>
<tr>
<td></td>
<td>2.2 - 4.1</td>
<td>53</td>
<td>15</td>
<td>0.91 (0.42 - 1.96)</td>
</tr>
<tr>
<td></td>
<td>&gt;4.1</td>
<td>52</td>
<td>16</td>
<td>0.92 (0.39 - 2.15)</td>
</tr>
<tr>
<td><strong>basic model + BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TotAPN</td>
<td>&lt;17.6</td>
<td>42</td>
<td>30</td>
<td>1 (reference)</td>
</tr>
<tr>
<td></td>
<td>17.6 - 28.8</td>
<td>59</td>
<td>14</td>
<td>0.34 (0.16 - 0.73)</td>
</tr>
<tr>
<td></td>
<td>&gt;28.8</td>
<td>59</td>
<td>14</td>
<td>0.29 (0.13 - 0.66)</td>
</tr>
<tr>
<td>HmwAPN</td>
<td>&lt;2.2</td>
<td>51</td>
<td>17</td>
<td>1 (reference)</td>
</tr>
<tr>
<td></td>
<td>2.2 - 4.1</td>
<td>53</td>
<td>15</td>
<td>0.91 (0.41 - 1.99)</td>
</tr>
<tr>
<td></td>
<td>&gt;4.1</td>
<td>52</td>
<td>16</td>
<td>0.91 (0.38 - 2.15)</td>
</tr>
</tbody>
</table>

**Figure 3.** Associations of baseline total adiponectin (totAPN) and high molecular weight adiponectin (hmwAPN) levels with radiographic progression in patients with hand osteoarthritis (HOA). A. Generalized estimating equations analysis between tertiles of adiponectin in patients with HOA (Genetics ARthrosis and Progression cohort analyses) were corrected for age, sex, treatment strategy, and body mass index (BMI). Concentrations of adiponectin are expressed in µg/ml. Difference in sum of joint space narrowing (ΔJSN) between baseline and followup are depicted for tertiles of totAPN (B) and hmwAPN (C). Significance was calculated using Mann-Whitney U test. A p value < 0.05 was considered significant.