Chapter 6

Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis

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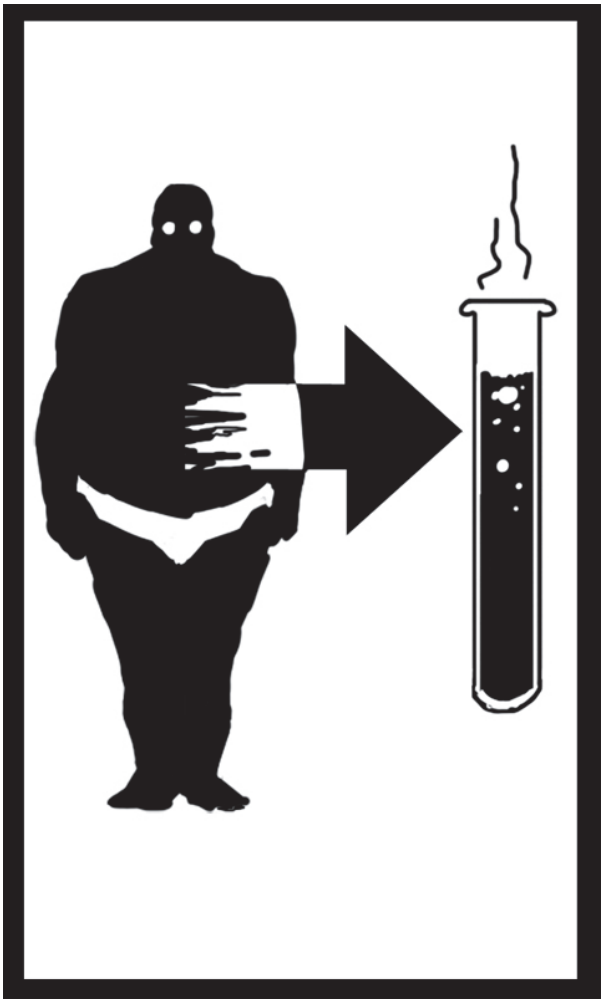

Published in:
Annals of Rheumatic Disease.
2011 Jul;70(7):1282-4

ABSTRACT

Objective

To investigate the association between baseline serum adipokines levels—leptin, adiponectin and resistin—and long-term progression of hand osteoarthritis (HOA).

Methods

Baseline and 6-year radiographs of 164 patients (mean age 60 years, 81% women) with HOA (defined as a Kellgren and Lawrence score ≥2 in at least two hand joints) were assessed for joint space narrowing (JSN) in 32 hand joints using the Osteoarthritis Research Society International atlas. Progression was defined as a change in the sum of the JSN score above the smallest detectable change of 2, reflecting change above measurement error. Serum adipokines were measured at baseline and patients were categorised by adipokine tertiles. RRs (and 95% CI) of HOA progression for patients in the second and third tertiles were calculated relative to the first tertile, using generalised estimating equations. Adjustments were made for age, sex and body mass index.

Results

Patients in the two highest tertiles of adiponectin had a decreased risk of 70% (RR=0.3 (0.2 to 0.7)) for HOA progression in comparison with patients in the lowest tertile. Leptin and resistin levels were not associated with progression.

Conclusion

A higher adiponectin level seems to be protective against progression of HOA.

6.1. INTRODUCTION

Obesity is a well-known risk factor for osteoarthritis (OA).[1] The link between being overweight and OA may be explained by the increased joint stress accompanying obesity. However, the mechanical burden does not explain the observation that being obese is also associated with OA of non-weight bearing joints such as hand joints.[2] This observation suggests that systemic factors associated with obesity play a role in the pathophysiology of OA.[3]

Leptin, adiponectin and resistin are among the systemic factors implicated in obesity. These adipokines are produced by adipocytes but may also be synthesised at other sites.[4,5] Adipokines are involved in a wide range of physiological processes in the human body, including immunity, bone mass function and glucose homoeostasis.[4,6] In OA, studies on the role of adipokines are emerging. However, data mostly originate from experimental or cross-sectional studies which use knee OA as phenotype.[3] Arguably, knee OA is less suitable for studies on metabolic factors associated with obesity in OA because the knee is also influenced by mechanical force associated with obesity.

Therefore, it is difficult to differentiate between metabolic and mechanical factors in obese subjects. Therefore, we investigated the association between baseline serum levels of leptin, adiponectin and resistin and radiographic progression of hand OA over 6 years.

6.2. PATIENTS AND METHODS

6.2.1. Study design and patient population

The study was conducted in 248 participants of the Genetics, ARthrosis and Progression (GARP) study with hand OA. The GARP study included 192 Caucasian sib pairs (aged 40 to 70 years) from primary or secondary care; all had symptomatic OA at multiple joint sites in the hands or in two or more of the following joint sites: hand, spine (cervical or lumbar), knee, or hip.[7] Hand OA was defined as Kellgren and

Lawrence score ≥2 (appendix C.1) in at least two hand joints. The GARP study was approved by the medical ethics committee of the Leiden University Medical Center.

6.2.2. Radiographs and definition of progression

Standardised protocols were used to obtain the radiographs of hands (dorsal-volar) at baseline (August 2000 to March 2003) and at follow-up (April 2007 to June 2008).

Two experienced readers (EY, JB) who were blinded for patient characteristics scored the radiographs paired in chronological order by using the Osteoarthritis Research Society International (OARSI) atlas (appendix C.2).[8] Joint space narrowing (JSN) was graded 0 to 3 in 32 joints of both hands: distal interphalangeal, proximal interphalangeal, first interphalangeal, first carpometacarpal, metacarpophalangeal and scaphotrapezotrapezoidal joints, leading to a sum score of JSN, ranging from 0 to 96. The intraclass correlation coefficient for intrareader reproducibility based on a random sample of 25 radiographs was very good: 0.87. Progression was defined as the difference between the sum of the JSN scores at follow-up and at baseline above the smallest detectable change (SDC). The SDC reflects change above measurement error.[9] We chose JSN as the outcome since it reflects articular cartilage damage.[10] Since the SDC was 1.5, a JSN score change ≥2 was defined as progression.

6.2.3. Assays

Baseline serum adipokine concentration was measured using the Bio-Plex Pro Human Diabetes kit (Bio-Rad, Hercules, CA, USA), the Bio-Plex array reader and Bio-Plex software, following the manufacturer's instruction. The intra-assay and interassay variations for leptin are 3% and 4%, respectively; for adiponectin 4% and 2% and for resistin 3% and 4%. All blood samples were obtained in the morning.

6.2.4. Statistical analysis

All analysis was performed using PASW Statistics 17 (SPSS Inc, Chicago, Illinois, USA). Means (SD) were used to describe baseline characteristics. The association between body mass index (BMI) and progression of hand OA was evaluated using logistic regression analysis. The correlation among adipokines and the correlation between

BMI and adipokines were evaluated using Pearson's correlation coefficient (with p values).

The geometric mean difference (95% CI) in adipokine levels between patients with and without progression was estimated using generalised estimating equations with robust variance estimators to account for family effects and corrected for age, sex and BMI. Geometric mean was calculated because in this analysis, the adipokine levels were log-transformed owing to the skewed distributions.

In the absence of established cut-off points and in order to retain adequate statistical power, we categorised patients by adipokine tertiles. ORs of hand OA progression for patients in the second and third tertiles were calculated relative to the first tertile, using generalised estimating equations. ORs were subsequently transformed to RRs (95% CI) because ORs for common outcomes in a fixed cohort are not a good approximations of RRs.[11] Adjustments were made for age, sex and BMI. RRs >1 indicate a higher risk for progression.

6.3. RESULTS

6.3.1. Study population

Of the 248 patients with hand OA, 208 (83.9%) gave consent for follow-up. Nine patients had died and 31 did not give consent. The most common reasons for lack of consent were loss of interest, health problems not related to OA and unavailability of transport. From patients who gave consent, complete radiographs at baseline and follow-up were available from 164 patients.

The mean follow-up time was 6.0 years (SD 0.6 years). Baseline characteristics are shown in table 6.1. Patients without complete radiographs were somewhat older. Other demographic and disease characteristics did not differ between these groups (data not shown).

Fifty-five of the 164 patients showed progression of hand OA. BMI was not associated with progression (OR=1.003 (95% CI 0.9 to 1.1)). Leptin, adiponectin and resistin levels did not correlate with each other. BMI was positively correlated with leptin (Pearson's correlation coefficient: 0.3, p=0.00) and resistin (0.2, p=0.04), and negatively correlated with adiponectin (−0.2, p= 0.005).

Table 6.1 Baseline characteristics (n=164).

Characteristics	
Mean age, years (SD)	60 (7)
Number of female, %	133 (81)
Mean BMI, kg/m^2 (SD)	27.4 (5.1)
Number of patients with Osteoarthritis on other sites[1] (%)	
Knee	74 (45.1)
Hip	44 (26.8)
Mean baseline serum level (SD)	
Leptin, ng/mL	8.3 (7.9)
Adiponectin, µg/mL	25.4 (16.3)
Resistin, ng/mL	1.3 (0.8)

[1] defined on radiograph as knee or hip with Kellgren and Lawrence score.

6.3.2. Association between adipokines and hand OA progression

The mean leptin level in patients with hand OA progression was slightly higher than in patients without progression: 3.0 ng/ ml (95% CI −0.3 to 6.3), p=0.08. The mean adiponectin level was significantly lower (−6.0 µg/ml (−11.3 to −0.8), p=0.02) in patients with progression compared with those without progression. The mean resistin levels did not differ across hand OA progression groups: −0.04 ng/ml (−0.3 to 0.2), p=0.8.

After adjusting for age, sex and BMI, patients in two highest tertiles of adiponectin had a 70% decrease in risk (RR (95% CI) 0.3 (0.2 to 0.7)) for hand OA progression in comparisonto patients in the lowest tertile (table 6.2). The RRs were similar when leptin and resistin levels were added to the model. Leptin and resistin levels were not associated with progression. Patients in the highest tertile of leptin and resistin levels had RR=1.1 (0.5 to 1.9) and 0.8 (0.3 to 1.4), respectively, of having hand OA progression.

Table 6.2 The association between adipokines and progression of hand osteoarthritis.

Serum level of adipokines	Number of patients		Crude RR (95% CI)	RR after adjusting with age, sex and BMI (95% CI)
	With progression (n=55)	Without progression (n=109)		
Leptin (ng/mL)				
< 4.4	16	34	1 (reference)	1 (reference)
4.4 to 8.2	13	36	0.9 (0.4 to 1.5)	0.8 (0.4 to 1.4)
> 8.2	20	31	1.2 (0.7 to 1.9)	1.1 (0.5 to 1.9)
Adiponectin (μg/mL)				
< 16.6	26	24	1 (reference)	1 (reference)
16.6 to 28.4	10	38	0.3 (0.1 to 0.6)‡	0.3 (0.2 to 0.7)‡
> 28.4	10	38	0.3 (0.1 to 0.6)‡	0.3 (0.2 to 0.7)‡
Resistin (ng/mL)				
< 0.8	19	34	1 (reference)	1 (reference)
0.8 to 1.4	16	32	0.9 (0.5 to 1.5)	0.9 (0.5 to 1.5)
> 1.4	14	33	0.9 (0.4 to 1.5)	0.8 (0.3 to 1.4)

6.4. DISCUSSION

As far as we know, this is the first report that shows that a higher level of adiponectin is associated with a lower risk for hand OA progression. Adiponectin appears to be protective against cartilage damage. The other adipokines we investigated showed no association with hand OA progression.

Our result differs from the only other clinical study investigating adiponectin and hand OA, where it was shown that the mean serum level of adiponectin was higher in 48 women with, than in 27 women without, erosive hand OA in a cross-sectional analysis.[12] The discrepancy might be caused by the difference in the research questions, in case definitions and in study designs. In a cross-sectional study, it is not possible to draw any conclusion about causation. Our result is also contradictory to the result from a study in patients with rheumatoid arthritis (RA), where higher adiponectin levels were shown to be associated with more radiographic damage in a cross-sectional analysis.[13] This difference can be explained by the difference in the radiological scoring system, where in RA bone erosion was assessed next to JSN. Moreover, the difference might also caused by the difference in the underlying biological processes between OA and RA.

The mechanisms that may explain the protective role of adiponectin may be direct and indirect. A possible direct mechanism is the induction of tissue inhibitor of metalloproteinase-2, which consequently reduced the cartilage defect induced by matrix metalloproteinase.[14] A putative indirect mechanism is by mediation of atherosclerosis. It is speculated that atherosclerotic plaques might obstruct the subchondral vasculature and subsequently impair cartilage nutrition, leading to its deterioration.[15] Since adiponectin is protective against atherosclerosis, [16] the presence of a high level of adiponectin might prevent cartilage deterioration.

Our results showed no association between leptin and resistin levels and hand OA progression. Filkova and colleagues also showed previously that there was no difference in serum level of resistin between patients with and without erosive hand OA.[12] The association between leptin levels and hand OA, to our knowledge has not been investigated previously. Experimental data on the role of leptin on cartilage are also inconclusive. Catabolic [4,17] and anabolic [18] effects have been reported. In our study, the effect of adiponectin on hand OA progression remains after adjustment for BMI, and BMI itself is not associated with progression. This is not surprising if we consider that BMI is simply an algorithm of the weight of a person corrected for height. It does not differentiate total body fat from lean body mass.[19] BMI might be not as informative as measurement of fat tissue products in evaluating the effect of fat tissue.

In conclusion, our findings might provide insight into the potential importance of adiponectin in OA. Although our results should first be confirmed in other studies, they indicate that adiponectin is an attractive target for prevention of hand OA progression since adiponectin levels can be increased through pharmaceutical and lifestyle intervention.[5]

Acknowledgements

The authors would like to acknowledge support of the cooperating hospitals (Bronovo Hospital, The Hague: Dr ML Westedt; Jan van Breemen Instituut, Amsterdam: Dr D van Schaardenburg; Leyenburg Hospital, The Hague: Dr HK Ronday and Dr LN Coene;

Reinier de Graaf Gasthuis, Delft: Dr AJ Peeters; Rijnland Hospital, Leiderdorp: Dr EJ van Langelaan) and referring rheumatologists, orthopaedic surgeons and general practitioners.

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