Hypothesis

# Adipose Tissue as a Modulator of Clinical Inflammation: Does Obesity Reduce the Prevalence of Rheumatoid Arthritis?

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*ABSTRACT.* ***Objective.*** Obese individuals display circulating proinflammatory cytokine elevations similar to those in patients with rheumatoid arthritis (RA). We wished to determine if extremely obese individuals were overrepresented among a group of patients with RA.

***Methods.*** We performed both multi- and univariate analyses of data from a large, community-based population attending the "wellness" clinic of a large health maintenance organization in Southern California. We also examined the data from 5 other studies that examined the relationship between various environmental factors and the incidence and prevalence of RA.

***Results.*** We found no relationship between the prevalence of RA and body mass index (BMI) in our own data or in the preponderance of previously published studies examining the same question.

***Conclusion.*** Although both RA and obesity have been reported to be characterized by high serum levels of inflammatory cytokines, the frequency of one disorder was not increased in the other. We propose that the lack of association in prevalence between the 2 inflammatory states, rather than reflecting a post-hoc effect of the disease on BMI, is a function of the relative amounts of pro- and antiinflammatory mediators produced in adipose tissue, which under many circumstances leads to an overall systemic antiinflammatory tone. (First Release Feb 15 2007; J Rheumatol 2007;34:488–92)

*Key Indexing Terms:*
OBESITY RHEUMATOID ARTHRITIS CYTOKINES INFLAMMATORY TONE

For many diseases, obesity is considered a complicating factor or even causative. Over 1000 published studies have documented the correlation between obesity, the metabolic syndrome, type 2 diabetes mellitus, and inflammation. Obesity is characterized by elevated circulating C-reactive protein (CRP), interleukin 1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α)[1] secreted from white adipocytes together with other adipokines such as leptin and adiponectin[2].

Rheumatoid arthritis (RA) is both a local and systemic inflammatory disease. It too is associated with elevated serum CRP, IL-1, IL-6, and TNF-α[3,4]. Current treatment of RA utilizes immunosuppressive agents, anti-TNF antibodies, TNF receptor and IL-1 receptor antagonists, all aimed at reducing production of proinflammatory cytokines or preventing the peptides from engaging their receptors[4,5]. The literature regarding the relationship of the 2 conditions is unsettled, with the majority of, but not all, studies failing to show an association of RA prevalence or incidence with body mass index (BMI) greater than 26[6-12]. To get a better sense of the interaction between obesity and RA in our community, we examined data available from Kaiser Permanente of San Diego, a major health provider in Southern California.

## MATERIALS AND METHODS

The data analyzed reflect information concerning a cohort of more than 41,000 individuals, ages 20–97 years, who attended the Kaiser health appraisal clinic from May 1998 to August 2001[13]. In order to eliminate potential ethnic differences in either BMI or the prevalence, and because 78.7% of the Kaiser-utilizing community self-reported their ethnicity as "White," the analysis was limited to that cohort. The entire population was 7.2% self-identified Hispanic, 3.6% African American, 4.4% Asian, and 6.2% other or mixed race.

International Classification of Diseases, Ninth Revision codes from inpatient records available for the cohort for the years 1995 to 2004 were used to identify cases of RA (code 7140) and osteoarthritis (OA; code 715). Denominators represent all subjects in the cohort who had at least one hospitalization during the same period. While diagnoses defined in this manner are not as precise as in incidence studies employing American College of Rheumatology (ACR) criteria, the overall prevalence of both OA and RA were consistent with data available for the general US population[14].

Our evaluation of obesity utilized BMI categories based on US government definitions of underweight (< 18.5), normal weight (18.5–24.9), overweight (25–29.9), and obese (≥ 30)[15].

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We found no association between the prevalence of RA and obesity as defined by a BMI ≥ 30 kg/m$^2$ (Table 1). The lack of association between RA and obesity was confirmed in multivariate models controlling for age and smoking status (Table 2).

In the same cohort, another disease leading to joint destruction, but with less evidence of systemic inflammation, OA of the knee, shows the previously documented highly significant positive association with obesity (Table 3). The lack of association of OA of the hip or of the hand with obesity was consistent with reports supporting the notion that OA at the knee is more influenced by the local biomechanical effects of excess weight[16,17].

## RESULTS

Five other studies have addressed the association between RA and obesity (Table 4). Our finding of no significant association between RA and obesity is consistent with the findings of the largest of the 3 case-control studies and both the large prospective studies[7,10,12]. All the studies listed in Table 4 have the advantage of including only incident cases of RA. They avoid the potential confounding effect of weight loss that may occur as a result of RA, which cannot be addressed in a cross-sectional study such as ours. Based on prevalence data alone, one might be inclined to believe that chronic inflammation would be associated with weight loss and a higher prevalence of RA in extremely thin individuals despite the shared profiles of inflammatory mediators. There are data suggesting that individuals with severe disease can lose weight and muscle in the course of the disease, so-called rheumatoid cachexia[18,19]. While a significant number of individuals with this phenotype might bias prevalence data, it is unlikely to affect an estimate of incidence, hence the concordance of our prevalence with the reported incidence data was reassuring.

Given the recent emergence of knowledge establishing the nature of adipose tissue as an inflammatory organ, the fact that 2 prospective studies and the most recent case-control study, involving approximately 1000 newly diagnosed cases of the disease, did not show a relationship between obesity and RA is noteworthy. In the largest of the studies the investigators examined the relationship among several environmental factors and RA. They found that the frequency of BMI > 25 was no higher in individuals diagnosed with RA defined by ACR criteria over a 5-year period in Sweden than in controls. Not surprisingly, the authors of this report, as well as those of the 2 other analyses with similar results, made no comment regarding the relationship, or lack thereof, between obesity and RA. Negative findings in a study are generally not emphasized unless they are unexpected or strongly support the inves-

*Table 1.* Prevalence of RA among Whites by BMI, sex, and age.

| BMI (kg/m$^2$) | White Men | | White Women | |
|---|---|---|---|---|
| | Overall (%) | ≥ 55 yrs (%) | Overall (%) | ≥ 55 yrs (%) |
| < 18.5 | 1/18 (5.6) | 1/17 (5.9) | 2/64 (3.1) | 2/44 (4.5) |
| 18.5–24.9 | 12/1498 (0.8) | 12/1183 (1.0) | 32/2799 (1.1) | 28/1789 (1.6) |
| 25–29.9 | 24/3405 (0.7) | 21/2647 (0.8) | 21/2490 (0.8) | 19/1781 (1.1) |
| ≥ 30 | 9/1988 (0.5) | 8/1449 (0.6) | 17/2104 (0.8) | 14/1367 (1.0) |

*Table 2.* Multivariable association of BMI with prevalence of RA in white adults.

| Factor | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p | OR | 95% CI | p |
| Age (10 yr interval) | 1.08 | 1.05–1.11 | < 0.0001 | 1.06 | 1.04–1.08 | < 0.0001 |
| Smoking status (ever vs never) | 1.74 | 0.93–3.25 | 0.085 | 2.45 | 1.52–3.93 | 0.0002 |
| BMI* | 0.95 | 0.88–1.02 | 0.15 | 0.99 | 0.95–1.04 | 0.86 |
| Obesity* | 0.71 | 0.34–1.48 | 0.36 | 0.98 | 0.57–1.67 | 0.94 |

* Tested in separate models as a continuous variable (BMI) or a dichotomous variable (obese vs not obese), controlling for age and smoking status.

*Table 3.* Prevalence of osteoarthritis among Whites by BMI, sex, and age.

| BMI (kg/m$^2$) | White Men | | White Women | |
|---|---|---|---|---|
| | Overall (%) | ≥ 55 yrs (%) | Overall (%) | ≥ 55 yrs (%) |
| < 18.5 | 3/18 (16.7) | 3/17 (17.6) | 3/64 (4.7) | 3/44 (6.8) |
| 18.5–24.9 | 161/1498 (10.7) | 143/1183 (12.1) | 252/2799 (9.0) | 228/1789 (12.7) |
| 25–29.9 | 450/3405 (13.2) | 395/2647 (14.9) | 353/2490 (14.2) | 320/1781 (18.0) |
| ≥ 30 | 354/1988 (17.8) | 301/1449 (20.8) | 381/2104 (18.1) | 332/1367 (24.3) |

*Table 4.* Studies examining the association between RA and obesity.

| Study Site | Years | RA Cases, n | Controls, n | Association Between RA and Obesity Relative Risk (95% CI) | Association Between RA and Smoking Relative Risk (95% CI) | Reference |
|---|---|---|---|---|---|---|
| Prospective studies | | | | | | |
| US | 1976–84 | 115 | 116,664 | 1.1 (0.7–1.9) | 1.5 (0.9–2.3) | Hernandez-Avila[7] |
| US | 1986–97 | 158 | 31,178 | 1.0 (0.7–1.6) | 1.7 (1.0–3.0) | Cerhan[10] |
| Case-control studies | | | | | | |
| US | 1986–91 | 349 | 1457 | 1.5 (1.0–2.3), premenopausal women<br>1.4 (0.7–2.6) postmenopausal women | 1.2 (0.8–1.7), premenopausal women<br>1.4 (0.9–2.2), postmenopausal women | Voigt[8] |
| UK | 1994–95 | 93 | 90 | 3.7 (1.1–12.3) | 1.7 (1.1–2.6) | Symmons[9] |
| Sweden | 1996–2001 | 843 | 627 | 1.0 (0.8–1.2) | 1.5 (1.2–2.0) | Padyukov[12] |

tigators' conclusions. In contrast to these results, 2 earlier and smaller case-control studies, one from the UK and the other from the Pacific Northwestern US, suggested a possible association between high BMI and risk of RA[8,9]. It is not clear why the findings in these analyses differed from the others, although the result from the UK study had the largest 95% confidence interval. In the Pacific Northwest study the positive association reached significance only in premenopausal women, generally the most severely affected subset of patients with RA.

Interestingly, the positive association between smoking and RA in each of the studies was of a similar magnitude, although it did not reach significance in all. Analysis of our own data comparing prevalence of RA in smokers with nonsmokers, controlling for BMI, age, and sex, showed a positive association with smoking of approximately the same size as in the other studies, with an odds ratio (95% CI) of 1.7 (0.9, 3.3) in men and 2.5 (1.5, 3.9) in women. It is thus difficult to account for the differences observed in the effect of obesity on the development of RA on the basis of some technical aspect of any of the analyses. Our own observations and the significant number of participants suggesting no effect of extreme obesity on RA prevalence or incidence and to some extent the dissociation from the predisposing effects of smoking prompted us to consider the physiologic mechanisms possibly responsible for the lack of effect of obesity.

## DISCUSSION

The apparent dissociation of the 2 "inflammatory" diseases, obesity and RA, suggests that white adipocytes may secrete antiinflammatory mediators in excess of the proinflammatory mediators secreted by these cells. Adipocytes produce a large number of both pro- and antiinflammatory cytokines, and local effects in the adipose tissue have been described as predominantly inflammatory[20]. Serum sample analysis, however, shows high levels of IL-1ra in the circulation[21,22]. The higher levels of IL-1ra compared with IL-1ß is such that, at least with respect to the IL-1 receptor, an antiinflammatory tone may be present in obesity. The therapeutic effect of IL-1ra (anakinra/Kineret) in treatment of RA[23] as well as the spontaneous RA-like pathology in IL-1ra knockout mice[24] support the notion that IL-1, as well as TNF-α, is an important mediator in RA. The presence of large amounts of adipose tissue-derived IL-1ra in the circulation of obese subjects may lead to an IL-1ra/IL-1ß ratio such that in the absence of an external stimulus antiinflammatory signaling predominates, suppressing the onset of RA. The suppression, which may be critically dependent on this ratio, is reflected in its lower prevalence in the obese members of our study population as well as those in similar and more extensive studies[25].

An alternative hypothesis is that the inflammation associated with obesity has a preconditioning effect similar to that seen with bacterial lipopolysaccharide (LPS) exposure, in which prior exposure protects the animal from subsequent LPS toxicity by "desensitizing" Toll signaling[26,27]. Adipocytes produce several known stimulators of Toll signaling including IL-1, thus macrophages carrying IL-1 R1 may be partially desensitized by the circulating IL-1. It is well documented that IL-1 is a potent inducer of IL-1R, TNF, IL-6, and cyclooxygenase 2 (COX2), thus desensitization of IL-1 signaling may suppress manifestations of RA. Other adipokines and known and yet unidentified cytokines may play similar desensitizing roles for circulating macrophages and those that have entered the joints. Leptin, an important adipokine, induces suppressors of cytokine signaling (SOCS) and affects T helper cell (Th1-Th2) balance[28,29]. A recent study found that leptin levels were negatively correlated with inflammatory markers in RA, an observation consistent with the epidemiological findings (Tables 1 and 2)[30].

If obesity, one inflammatory disease, is not associated with the incidence and prevalence of RA, why should smoking, another condition in which chronic inflammation leads to cytokine production, increase the risk of acquiring RA? Perhaps in chronic smokers the production of proinflammatory cytokines, primarily in nonadipose tissue, in macrophages and endothelial cells of the lung and airways, so outstrips the synthesis and secretion of those with antiinflammatory activity by adipose tissue that the overall tone is inflammatory

rather than suppressive. It may simply reflect the fact that heavy smokers have less adipose tissue[31,32]. There would then be no antiinflammatory cytokine tone to counter the inflammatory events that ultimately lead to clinical RA. The universal finding of increased risk for RA in individuals who are heavy smokers or have a history of heavy smoking in the same analyses in which obesity does not increase one's risk would be consistent with such a concept.

While the issue of the relationship of the severity of RA to BMI cannot be addressed on the basis of our epidemiological data, several published studies and unpublished data from the Arthritis, Rheumatism, and Aging Medical Information System database suggest that obesity increases the severity of RA[33]. In contrast with those data, a recent study of 779 patients with RA diagnosed and followed by rheumatologists over a 7-year period suggests an inverse relationship between BMI and mortality, with a statistical interaction with inflammation as measured by erythrocyte sedimentation rate. However, the BMI effect was not statistically maintained when corrected for severity of RA and comorbidity[34]. These 2 sets of observations could be consistent, in that participants with the most severe RA (and increased mortality on the basis of severity) could be a cohort with relatively high BMI and overcome the effect seen in the context of the entire population. The apparent paradox between the differing influence of excess adipose tissue on the prevalence compared with the severity of RA could be explained if, under normal conditions, antiinflammatory cytokines were produced in excess of inflammatory cytokines in adipose tissue, but that once their effects were overcome by some peripheral inflammatory stimulus, with the attendant amplification of expression of proinflammatory molecules systemically, the manifestations of disease become more severe in a subset of patients (Figure 1). This subset of patients might be defined by polymorphisms of the IL-1ß and IL-1ra or other inflammation-associated genes that have been reported to influence RA severity[35].

Greater knowledge of antiinflammatory mediators present in obesity, and of the mechanisms by which they act, may open important new avenues for RA treatment. Conversely, it is possible that factors that contribute to the higher prevalence of RA in younger, lean White females prevent obesity. Identification of these factors would be as important as defining functional antiinflammatory mediators present in obesity.


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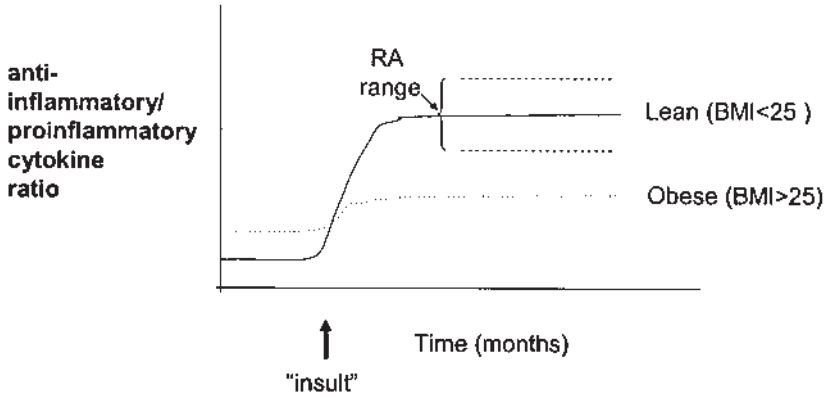


*Figure 1.* Hypothetical mechanism of lower prevalence of RA in obese individuals with high circulating cytokine levels. Prior to etiologic insult, obese individuals may have higher antiinflammatory/proinflammatory cytokines. Alternatively, they chronically display higher occupancy of cytokine receptors, blunting the response to the hypothetical insult that in lean individuals initiates the local increase in cytokine production required to establish ongoing inflammation (the "effective RA concentration").

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