Relation Between Body Mass Index and Radiological Progression in Patients with Rheumatoid Arthritis

JÖRG KAUFMANN, VOLKER KIELSTEIN, SUSANN KILIAN, GÜNTER STEIN, and GERT HEIN

ABSTRACT. ***Objective.*** To determine if there is an influence of body mass index (BMI) on the radiological progression in early and longer duration rheumatoid arthritis (RA).

Methods. Fifty-four patients with RA were observed in a progressive 2 year followup for radiological progression of joint damage. At the beginning of study, 27 (50%) patients had a duration of complaints less than 6 months, grouped as early RA. BMI at the beginning and end of the study were monitored, together with HLA-DRB1 alleles, initial joint erosions, duration of disease, age, sex, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Outcome was defined as radiographic damage according to yearly increase of Larsen score.

Results. Increased radiographic joint damage of patients was significantly correlated with lower BMI at the beginning of the study ($r = 0.363$, $p < 0.05$), the presence of initial joint erosions ($r = 0.341$, $p < 0.01$), ESR ($r = 0.315$, $p < 0.05$), and CRP at study entry ($r = 0.427$, $p < 0.01$). Patients with an increase of Larsen score $\geq$ 5.8/year were found to have a lower weight at the beginning of their complaints (BMI 24.8 ± 4.7 vs 27.8 ± 3.8; $p < 0.05$) as well as after the time of observation (BMI 24.6 ± 3.7 vs 27.6 ± 4.9; $p < 0.05$). Stepwise logistic regression analysis revealed a BMI < 27 at the beginning of disease (ß = 2.04, $p = 0.003$, odds ratio = 7.69), the presence of HLA-DR4 shared epitope (ß = 1.76, $p = 0.015$, OR 5.82), and joint erosions at study entry (ß = 1.56, $p = 0.044$, OR 4.78) as significant predictors for rapid joint damage.

Conclusion. Together with the presence of HLA-DR4 shared epitope and erosive disease at study entry, a low BMI at the beginning of RA was found in association with higher radiographic progression in RA. Accordingly, BMI could be of interest as a sensitive and inflammation-independent predictor for radiological outcome of RA. (J Rheumatol 2003;30:2350–5)

Key Indexing Terms:
RHEUMATOID ARTHRITIS BODY MASS INDEX SHARED EPITOPE
RADIOGRAPHIC DAMAGE

Rheumatoid arthritis (RA), occurring with a prevalence of ~1% in the population, is characterized by chronic inflammation of different joints. In particular, the small joints of hands and feet are often symmetrically affected[1]. Synovial joint tissue becomes infiltrated with a variety of lymphocytes and macrophages that combine with activated synoviocytes to form an aggressively growing pannus of proliferative tissue resulting in progressive destruction of cartilage and underlying bone, with the consequence of irreversible joint deformity and loss of joint function[2].

Extension and progression of joint destruction take a very heterogenous temporary course in patients. About 60–90% of patients with early RA have a rather progressive course of disease, usually with considerable joint destruction and functional disability[3,4]. In these patients most rapid progression of joint destruction occurs during the first 2 years[5-7]. Therefore, early identification of patients who will develop a rapid progressive course is particularly important for appropriate therapy in order to delay the destructive process and a worse functional outcome[8-11]. To date, instruments and measurable variables for quick and reliable assessments of disease progression in individual patients with early RA are not sufficiently developed.

Much research has recently been performed to recognize predictive factors indicating a worse radiological progression of RA. Variables that have been described may be divided into those directly associated with the process of inflammation such as concentrations of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), pro-matrix metalloproteinase-3, or the Health Assessment Questionnaire (HAQ) and those independent of the intensity of inflammation, such as rheumatoid factor (RF), HLA-DR4 status, age, sex, biomechanical stress, and duration of disease[5,12-18]. Conflicting data have been published regarding diagnostic value for some of these variables.

Recently, we investigated the relation between body mass index (BMI) and collagen degradation in RA synovial tissue. We quantified the hydroxypyridinium collagen crosslinks pyridinoline and deoxypyridinoline in synovial

From the Department of Internal Medicine IV, Division of Rheumatology and Osteology, Friedrich Schiller University of Jena, Jena, Germany.

J. Kaufmann, MD; V. Kielstein; S. Kilian; G. Stein, MD, Professor; G. Hein, MD, Professor.

Address reprint requests to Dr. med. J. Kaufmann, Department of Internal Medicine IV, Division of Rheumatology and Osteology, Friedrich-Schiller-University of Jena, Erlanger Allee 101, 07740 Jena, Germany.
E-mail: joerg.kaufmann@med.uni-jena.de

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tissue and its urinary excretion, and found both increased collagen crosslinking density in synovial tissue and increased urinary excretion of these crosslinks for patients with low BMI, and vice versa decreased content of crosslinks at high BMI independent of disease activity at the time of investigation[19]. As high levels of crosslinks in urine and in synovial tissue are considered characteristic for increased disease activity, and this apparently is linked to the BMI of patients, we investigated the association of BMI and radiographic progression and the possible role of BMI as a predictive factor for severe joint damage in RA.

MATERIALS AND METHODS

Patients. As part of a prospective study investigating predictive variables for course and outcome of polyarthritis, we followed all patients with RA fulfilling the American College of Rheumatology (ACR) criteria[20] within one year after presentation; 54 of 123 (43.9%) patients were identified as having RA. Epidemiological data are summarized in Table 1. Twenty-seven patients had early RA, with a duration of complaints less than 6 months, whereas the other patients had longer duration RA, with a mean duration of 5.6 ± 3.8 years. At the beginning of the study, 41 (75.9%) patients were treated with disease modifying antirheumatic drugs (DMARD) including antimalarial drugs (10 patients), sulfasalazine (6), methotrexate (17), intramuscular gold (2), and azathioprine (4). Selection of DMARD was adjusted to individual requirements. Twenty-three patients (42.6%) had received oral corticosteroids with low dose prednisone (5–10 mg daily) continuously. In 6 patients DMARD treatment had to be withdrawn because of side effects or drug inefficacy resulting in the use of another DMARD. Body weight and height were measured at the beginning of disease (for longer duration RA documented retrospectively) and after 2 years. BMI was calculated as weight divided by squared height, expressed as kg/m^2. For statistical analyses patients were stratified according to whether they had relatively low (BMI < 27) or high (BMI ≥ 27) body weight. During the study period there was no significant difference in DMARD and corticosteroid therapy between the low and high BMI groups. ESR (Westergren method) and CRP (nephelometry) were determined at the beginning and end of study.

HLA-DRB1 genotyping. Genotypes were obtained from leukocyte DNA samples derived from 5 ml of EDTA peripheral blood. HLA-DR subtypes were determined using FITC-conjugated monoclonal antibodies recognizing the HLA antigens (FACS method; HLA-DR4 subtyping kit, Medac Diagnostika, Hamburg, Germany)[21]. For logistic regression analysis patients were grouped dichotomously according to whether they carried the shared epitope (SE) or not.

Radiology. As an outcome variable for the irreversible joint destruction process, joint erosions were documented by means of radiography. At study entry and after 2 years hand and foot radiographs were taken, read in chronological sequence and in comparison with the initial radiograph, and scored by a single experienced observer (blinded to clinical information). Forty-two joints — the wrist and subtalar joints, 10 metacarpophalangeal, 8 proximal interphalangeal joints of the hands, 2 interphalangeal joints of the thumbs, 10 metatarsophalangeal joints, 8 interphalangeal joints of the feet, and 2 interphalangeal joints of the hallux—were analyzed. Each joint was graded on a 0 (normal joint) to 5 (mutilating destruction) point scale according to the method of Larsen[16], slightly modified by addition of 0.5 points when subchondral cysts were detectable (only grades 1 and 2). After multiplying the indices of subtalar and wrist joints by 5, the indices of the individual joints were added to form a general damage score between 0 and 250. Radiological progression, expressed as yearly increase of the Larsen score (ΔLS/year), was assessed by subtracting the initial Larsen score from the 2 year Larsen score, divided by 2. Patients were divided into 2 groups: "slow progression" and "rapid progression," using the smallest detectable ΔLS/year of 5.8[22].

Statistical analysis. Differences in means between groups were calculated using nonparametric tests for related variables (Wilcoxon rank-sum test or McNemar chi-square test) or nonrelated variables (Mann-Whitney U test). Correlations were carried out using the Spearman rank correlation method. The influence of clinical variables on the radiological outcome of disease progression was investigated by forward stepwise logistic regression analysis using ΔLS/year as the dependent variable. As independent variables, BMI, rheumatoid factor (IgM-RF) positivity, age at the beginning of disease, duration of disease at initial presentation, sex, the presence of HLA-DR4 SE, joint erosions at study entry, and initial values for ESR and CRP were included into this regression model. All calculations were performed using the statistical software package SPSS version 9.0.

RESULTS

Patients' characteristics. Within the 2 year followup, complete data were obtained from all 54 patients. Table 1

Table 1. Baseline and 2 year followup characteristics of patients with RA. Nonparametric tests for related samples (* Wilcoxon rank sum test; ** McNemar chi-square test) were performed for comparable characteristics at baseline and after 2 year followup.

Patient characteristics	Baseline	2 Year Followup	p
N	54	54	
Age at study entry, yrs, median (range)	56 (30–83)	—	
Duration of complaints < 6 mo, n (%)	27 (50.0)	—	
Female, n (%)	45 (83.3)	—	
Positive IgM-RF, n (%)	38 (70.3)	—	
DMARD therapy, n (%)	41 (75.9)	44 (81.5)	0.955**
Initial BMI, mean (SD)	26.2 (4.6)	26.5 (4.5)	0.790*
BMI ≥ 27, n (%)	25 (46.3)	22 (40.7)	1.000**
ESR, mm/h, mean (SD)	25.9 (22.2)	20.4 (16.6)	0.151*
CRP, mg/l, mean (SD)	19.4 (26.5)	8.6 (13.7)	0.002*
Erosions at study entry, n (%)	20 (37.0)†		
Yearly increase of Larsen score > 5.8, n (%)	—	23 (42.6)	
SE+, n (%)	31 (57.4)	—	

† Three patients with early RA had erosions at study entry. DMARD: disease modifying antirheumatic drug, BMI: body mass index, SE: shared epitope.

presents demographic, clinical, and laboratory data. CRP was found to be significantly decreased after the 2 year observation period (p = 0.002).

Comparison between BMI, disease variables, and radiographic joint progression. According to the smallest detectable ΔLS/year of 5.8[22], development of radiological joint damage was stratified as "slowly progressive" [ΔLS/year < 5.8, n = 31 (57.4%)] and "rapidly progressive" [ΔLS/year ≥ 5.8, n = 23 (42.6%)]. RA patients with ΔLS/year ≥ 5.8 were found to have a lower mean initial BMI (BMIi) of 24.8 ± 4.7 and end-of-study BMI 24.6 ± 3.7, compared to those with ΔLS/year < 5.8 (27.8 ± 3.8 and 27.6 ± 4.9, respectively). Differences were found to be significant (p < 0.05), as shown in Figure 1. The variables BMIi and end-of study BMI (r = 0.363 and 0.404, respectively), ESR (r = 0.315) and CRP at study entry (r = 0.427) and an erosive joint damage at study entry (r = 0.341) were in significant relation to radiographic progression, revealed by Spearman rank correlation. The BMI was found to be nearly constant within the observation period and did not correlate with the disease activity indicators.

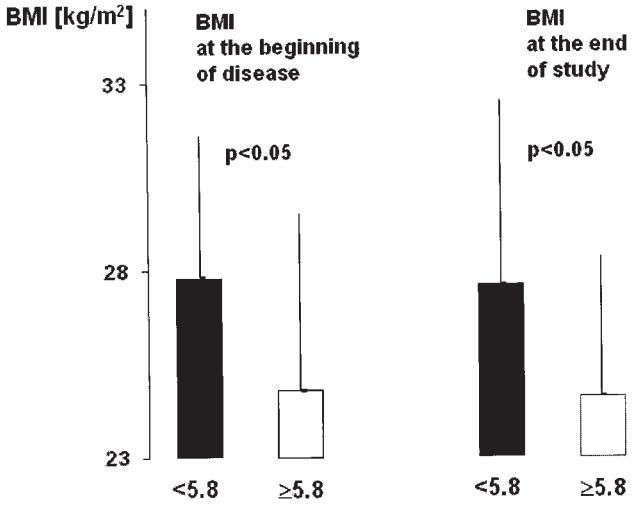

Figure 1. Comparison between patients with low and high radiographic joint damage (yearly increase of Larsen score < or ≥ 5.8) according to the BMI (Mann-Whitney U test). Significantly higher radiographic progression was found associated with low BMI at the beginning and end of the study, respectively.

Logistic regression analysis of BMI and other variables to predict severely progressive joint damage. Table 2 shows the results of logistic regression analysis for clinical variables on radiological progression. Variables with no influence on the ΔLS/year were removed from the model by forward stepwise deletion. In consequence, only a BMI < 27 at the beginning of disease (ß = 2.04, p = 0.0025), the presence of HLA-DR4 SE (ß = 1.76, p = 0.015), and the presence of erosive joint damage at study entry (ß = 1.56, p = 0.044) independently and significantly influence the radiological progression. The OR in this logistic regression model [OR_{lr} = Exp(ß)] for a radiological progression of ΔLS/year > 5.8 was found to be 7.69 for a BMI < 27 at the beginning of disease, 5.82 for the presence of the HLA-DR4 SE, and 4.78 for the preexistence of joint erosions. Initially determined low BMI (< 27) was found to predict severe radiological progression independently of the duration of complaints. Separate regression analyses for patients with duration of complaints both less and more than 6 months indicate analogous results for the predictive value of BMI < 27, the presence of shared epitope, and early erosions (data not shown). ESR and CRP at study entry were also significantly correlated with higher joint damage (r = 0.315, p < 0.05 and r = 0.427, p < 0.005, respectively), but have no additional value for the prediction of radiological progression.

DISCUSSION

Extension and progression of joint destruction in patients with RA do not show a unique picture. Progressive course of RA is seen in about 60–90% of patients with early RA[3,4], but the extent of joint destruction and resulting functional disability are very different. Progression of RA, which occurs particularly rapidly during the 2 years following first diagnosis[5-7], is obviously a multifactorially influenced

Table 2. Logistic regression analysis of disease variables that predicted greater radiographic progression as defined by yearly increase of Larsen score ≥ 5.8.

Criterion Predictor (n = 54)	ß Factor	Standard Error	Exp (ß) = OR_{lr}	95% CI	p
Constant	-2.49	0.81			0.002
Initial BMI < 27	2.04	0.67	7.69	4.83–14.57	0.003
HLA-DR4 SE+	1.76	0.72	5.82	2.96–11.13	0.015
Initial damage score	1.56	0.77	4.78	2.12–9.76	0.044
Variables not in the equation		> p			
Age	0.89	0.346			
CRP at study entry	0.11	0.735			
ESR at study entry	0.33	0.563			
RF-IgM (initially)	0.02	0.895			
Duration of complaints	0.05	0.826			
Female sex	0.01	0.938			

process. Predictive variables, as described, can be divided into factors directly associated with the process of inflammation and those independent of the actual intensity of inflammation in Table 3.

It has been generally accepted that best prediction of severe radiographic joint damage is associated with occurrence of early erosions[13,15] and with existence of the shared epitope on one or both DR4 alleles, carrying the amino acid sequences QKRAA and QRRAA in the binding groove of the MHC molecule[13,23,24]. Conflicting data have been published for the predictive value of other variables, such as ESR, CRP, HAQ, duration of complaints, sex, or IgM-RF[13–15,18,25-35]. This may be caused by different factors. First, the design of the studies is very heterogeneous and includes non-uniform inclusion criteria for patients, prospective and retrospective analyses, various scores and time intervals for the radiographic damage measurement, or different statistical methods[13,14,27,28]. Second, in addition to bias from different study designs, the heterogenous and periodic course of RA is a further reason for controversial results, especially for those predictive variables that are more or less dependent on disease activity. Accordingly, more definite results have been reported for disease activity-independent variables, such as HLA-DR status, early erosions, duration of disease, age at onset, or sex[13,15,29-34]. Ideal variables should predict radiographic outcome reliably, quickly, and independently of the actual disease activity.

In this regard, the influence of easily ascertainable body constitution markers such as BMI on RA has been given little attention. Obese patients are considered to have a higher relative risk to develop RA[36,37], although some investigators could not corroborate this coherence between overweight and incidence of RA[38]. The relation of obesity and functional ability in RA patients, which could be seen as an indirect link to joint damage, is also controversial. On one hand physical fitness was found to be slightly but significantly improved after controlled reduction of body weight by 4.5 kg[39], but in contrast female patients who lost more than 15% of their initial body weight were significantly more disabled as assessed by HAQ[40]. Investigations of relations between body weight and radiologically documented progression of RA are needed.

In our studies on crosslinking of collagen in RA synovial tissue[19] we investigated data about the influence of body weight on the progress of joint damage. In the present study RA patients were monitored for BMI and destruction of hand joints by radiographic controls over a period of 2 years. The data were evaluated by forward stepwise regression analysis including other disease-relevant variables, indicating significant correlation between patients' BMI and

Table 3. Variables reported in the literature concerning prediction of radiological progress in patients with RA.

Predicting Radiological Joint Progression	Not Predicting Joint Progression
Disease activity-dependent variables	
ESR (at study entry or mean value)[14]	ESR (at study entry or mean value)[27,28]
CRP (at study entry; mean value or time-integrated)[14, 15, 25, 29, 30]	CRP (at study entry or mean value)[31]
Pro-matrix metalloproteinase-3[14]	Serum orosomucoid[28]
Serum hyaluronate[47]	Serum C1 esterase inhibitor[28]
Clq[32]	Morning stiffness[13]
Mature, crosslinked carboxy terminal telopeptide of collagen I[48]	Swollen joint count[13, 15, 28, 31]
Mannose binding lectin[49]	Tender joint count[15]
HAQ[14]	Ritchie index[13]
Blood platelets[50]	HAQ[15]
	Disease Activity Score (DAS-28)[15]
	Grip strength of hands[13]
Disease activity-independent variables	
HLA-DR4 (DRB1-*04, *01, 1 or 2 positive alleles)[13, 29-31, 50, 51]	HLA-DR4 (DRB1- *04, *01, 1 or 2 positive alleles)[33, 34]
Sex[13, 34]	HLA-B27[28]
Biochemical stress[16, 43]	Duration of complaints/disease[15]
Early erosions (joint damage at study entry)[13, 15, 28]	Sex[15, 28]
BMI (from this study)	Age at onset of disease [13, 15, 28, 34]
	Rheumatoid nodules[33, 51]
Immunoglobulins	
IgA serum level[13]	Serum agalactosyl IgG[52]
Serum agalactosyl IgG[27]	RF-IgM[28-30, 33, 35]
RF-IgM[15, 27, 31, 32, 51]	RF-IgA[28, 35]
RF-IgG[27, 28]	RF-IgG[35]
Anti-Sa[29]	Anti-perinuclear factors[34,53]
Anti-CCP[54]	Anti-keratin[35]
Multifactorial score systems	
—	Sum of ACR criteria[28]

disease progression. Low BMI were positively associated with accelerated severe joint erosions, and higher BMI (≥ 27) are apparently correlated with slower progression in the joint destruction process. It seems that slight overweight of RA patients protects them from more rapid destruction of joints. Other disease-relevant variables, such as HLA-DR4 status and the inflammation markers ESR and CRP, were recorded in order to qualify any influence of a possible weight effect by them. This was especially important for the disease activity variables, because there are reports on the development of cachexia in RA patients due to disease activity[26,41,42]. Proinflammatory cytokines, such as tumor necrosis factor-alpha or interleukin 1, are known to play a key role for both inflammation-mediated loss of weight and joint destruction[17]. We did not observe a significant change of BMI related to disease activity, and BMI values at both beginning of disease and end of study were found to be in relation with the joint radiology. That indicates an association between low body weight and worse radiological outcome in RA, independent of the mean level of inflammation. Moreover, the relation between low BMI and increased joint destruction was found in both subgroups, those with early RA with duration of complaints less than 6 months and longer duration RA.

The mechanisms by which progression of damaged joints might occur regardless of disease activity are poorly understood. We suppose that obesity affects the destructive process on the level of joint structures. Adipocytes integrated in the architecture of synovial tissue might protect cartilage and the underlying bone from the destructive effect of local inflammation. A direct guarding function against collagen, the induced synthesis of a structurally altered and thus more protected collagen, or expression of antiinflammatory factors by adipocytes, such as adiponectin, are mechanisms that could explain any protective effects of adipocytes in synovial tissue[44,45]. Such a possible influence of adipocytes in synovial tissue on joint destruction was also observed by us in experimental studies of collagen degradation in obese patients with RA. We found the hydroxypyridinium collagen crosslinks pyridinoline and deoxypyridinoline decreased in hydrolysates of synovial tissue and in urine obtained simultaneously from overweight RA patients compared to those of normal or lower weight, independent of disease activity. Adipocytes were found to be tightly packed in synovial tissue of obese patients[19]. This lower occurrence of crosslink markers in synovial tissue of obese RA patients and in their urine reflects an inhibited collagen degradation and supports the clinical finding of decreased radiographic joint damage.

Our study provides the first data characterizing BMI as a factor with significant influence on the radiological outcome of RA, independent of the mean disease activity. Low BMI was found to be associated with worse radiological joint damage, whereas a relatively high BMI apparently delays the process of aggressive joint destruction. It is possible that BMI will be found to be a reliable method to predict the radiological outcome of RA. The diagnostic value of the readily measurable BMI for estimation of the individual risk of patients with RA confronted with progressive early joint damage should be verified in studies with higher numbers of patients.

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