ORIGINAL ARTICLE

Associations between parameters of nutritional status and disease activity in patients with rheumatoid arthritis

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KEY WORDS

disease activity, nutritional status, prognosis, rheumatoid arthritis, rheumatoid cachexia

ABSTRACT

INTRODUCTION In patients with rheumatoid arthritis (RA), the loss of body cell mass is observed, known as rheumatoid cachexia. Cachexia is associated with increased morbidity and premature mortality of RA patients.

OBJECTIVES The aim of the study was to assess the effect of chronic inflammation and disease activity on nutritional status in RA patients.

PATIENTS AND METHODS In 140 patients with RA (111 women, 29 men), RA activity was measured using the Disease Activity Score in 28 joints (DAS28) and using the Modified Health Assessment Questionnaire (M-HAQ). The nutritional status was assessed with the following parameters: serum albumin and total cholesterol (TC), body mass index (BMI), hand-grip strength (HGS), and tricipital skinfold thickness.

RESULTS There was a significant association between the parameters of nutritional status and the markers of inflammatory disease activity (number of swollen and tender joints, C-reactive protein, hemoglobin) and physical disability (M-HAQ). Swollen joint count and M-HAQ were inversely correlated with several nutritional parameters. In patients with high disease activity, significantly lower HGS and serum albumin levels were observed. Advanced stages of the disease (erosive and/or long-standing RA) were associated with lower HGS and higher TC levels.

CONCLUSIONS The nutritional status of RA patients is determined by the intensity of chronic inflammatory process observed in the course of the disease and by disease duration.

INTRODUCTION Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory disease characterized by symmetrical, destructive polyarthritis and is accompanied by systemic manifestations, including fatigue and cachexia. Rheumatoid cachexia is defined as loss of body cell mass (BCM), predominantly skeletal muscles, in the presence of stable or increased fat mass.[1-4] Development of rheumatoid cachexia is associated with excess production of proinflammatory cytokines, particularly tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β), accelerated protein catabolism, and low physical activity.[1,5] It develops in the presence of normal protein and energy intake, in the absence of clinically evident malabsorption, liver or renal dysfunction.[5] Cachexia appears to be a common metabolic consequence of RA, affecting up to ⅔ of all patients with RA; however, it is underdiagnosed in clinical practice.[1,3-4] Rheumatoid cachexia is thought to be an important contributor to increased morbidity and premature mortality in RA patients.[2,5]

The aim of the study was to assess the effect of chronic inflammation and disease activity on the nutritional status in RA patients.

PATIENTS AND METHODS The study group consisted of 140 consecutive patients with RA treated in the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Poland. The informed consent was obtained from the patients according to the Declaration of Helsinki. The design of the study was approved by the Ethical Committee of the Medical University

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Received: December 16, 2010.
Revision accepted: March 29, 2011.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2011; 121 (4): 122-128

TABLE 1 Baseline characteristics of patients with rheumatoid arthritis

Variables	Results
demographic	
age, y	50.3 (10.9) (range 19–76)
sex, women/men	111 (79.3%)/29 (20.7%)
RA-related	
disease duration, mo	120.6 (89.8) (range 6–396)
RA duration ≥10 years	64 (45.7%)
RF-IgM positivity	61 (70.7%)
ACPA positivity	116 (82.9%)
erosions	117 (83.6%)
extra-articular symptoms	58 (41.4%)
DAS28	4.52 (1.3) (range 1.88–8.5)
DAS28 >5.1	42 (30%)
M-HAQ	1.25 (0.62) (range 0–2.8)
clinical	
BMI, kg/m^2	24.6 (3.8) (range 16–38)
weight, kg	66.9 (12.5) (range 40.5–105)
waist circumference, cm	84.6 (10.8) (range 59–121)
TSF, mm	17.9 (6.5) (range 3.5–34.5)
HGS, kg	28.4 (19.2) (range 1–115)
laboratory	
CRP, mg/l	19.5 (22.5) (range 0.1–116)
ESR, mm/h	35.9 (24.3) (range 5–102)
Hb, g/dl	12.5 (1.3) (range 9.2–16.4)
total protein, g/dl	7.1 (0.6) (range 4.2–8.4)
albumin, g/dl	4.2 (0.4) (range 2.3–5.0)
fibrinogen, g/l	4.8 (1.3) (range 2.0–9.0)
glucose, mg/dl	94.7 (19.6) (range 54–213)
total cholesterol, mg/dl	200.9 (45.2) (range 98–365)
HDL cholesterol, mg/dl	59.9 (15.8) (range 32–115)
LDL cholesterol, mg/dl	117.4 (34.9) (range 38–245)
triglycerides, mg/dl	117.4 (55.55) (range 24–300)

Values are mean (SD) or numbers (percentage)

Conversion factors to SI units are as follows: for albumin – 10, fibrinogen – 0.01, glucose – 0.05551, hemoglobin – 0.6205, cholesterol – 0.02586, total protein – 10, and triglycerides – 0.0114

Abbreviations: ACPA – anticitrullinated peptide antibodies, BMI – body mass index, BP – blood pressure, CRP – C-reactive protein, DAS28 – disease activity score in 28 joints, ESR – erythrocyte sedimentation rate, Hb – hemoglobin, HDL – high-density lipoprotein, HGS – hand-grip strength, LDL– low–density lipoprotein, M-HAQ – modified health assessment questionnaire, RA – rheumatoid arthritis, RF-IgM – IgM rheumatoid factor, SD – standard deviation, TSF – tricipital skinfold thickness

of Lublin. All patients fulfilled the American College of Rheumatology classification criteria for RA.[6]

Clinical assessments Disease activity was assessed with the Disease Activity Score (DAS28), calculated from the number of tender and swollen joints, erythrocyte sedimentation rate (ESR), and the patient global assessment of health measured on a visual analogue scale (0–100).[7] High disease activity was defined as DAS28 >5.1 and low/moderate disease activity as DAS28 ≤5.1. Ability to perform daily activities was assessed using the Modified Health Assessment Questionnaire (M-HAQ) with the range of 0 to 3 (0 representing no impairment of function).[8] Erosive form of RA was diagnosed in those patients, who presented erosions on joint surfaces of bones in the radiograms of the hands and/or feet.

Body composition measurements Height and weight were measured barefoot wearing light clothes. Body mass index (BMI) was calculated as the ratio of weight and squared height. Tricipital skinfold thickness (TSF) was measured in both upper limbs, in the mid-point between the acromion and olecranon with the Harpenden caliper. The mean of these 2 measures was calculated for every patient. Waist circumference was measured in a standing position, at the umbilicus level. Hand-grip strength (HGS) was measured using the Harpenden dynamometer. The subjects were instructed to apply as much hand-grip pressure as possible. The results of HGS were expressed as the sum of the right and left side.

Laboratory tests Blood was collected after an overnight fasting to determine the complete blood cell count, ESR, serum concentrations of C-reactive protein (CRP), total protein, albumin, fibrinogen, glucose, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides at the University Hospital central laboratory. The atherogenic index was calculated as the ratio of TC and HDL cholesterol. Serum level of CRP was measured by immunoturbidimetric assay, with 1 mg/l as the upper limit of the normal range. Serum albumin was measured by a photometric test with bromocresol green (normal range: 3.8–5.1 g/dl). Serum levels of TC, HDL, and triglycerides were also measured using the standard enzymatic technique (BIOMAXIMA, Poland) and LDL cholesterol was calculated according to the Friedewald formula. Assessment of RA serological markers was performed: immunoglobulin (Ig) M-rheumatoid factor (RF-IgM) and anticitrullinated peptide antibodies (ACPA). RF-IgM was determined using the antirheumatoid factor ELISA (IgM) test (EUROIMMUN, Germany) with the recommended upper limit of the normal range 20 units (RU)/ml. ACPA were determined using the QUANTA Lite CCP3.1 IgG/IgA ELISA assay (INOVA Diagnostics, United States); normal values <20 U/ml.

Statistical analysis Results were expressed as mean (standard deviation, SD) or number (%). Variables were tested for normality by the Kolmogorov-Smirnov's test. Group differences were tested using the Student *t* test and Mann-Whitney test for normally and nonnormally distributed parameters, respectively. Multivariate analysis of variance (MANOVA, Wilks' λ test) was performed to verify whether the changes in the independent variables had significant effects on the dependent variables (parameters of nutritional status). BMI

TABLE 2 Characteristics of treatment used in the therapy of 140 patients with rheumatoid arthritis

no DMARDs	5 (3.6%)
nonbiological treatment (monotherapy or combined)	99 (70.7%)
MTX	53 (37.9%)
leflunomide	47 (33.6%)
chloroquine	11 (7.9%)
sulfasalazine	10 (7.1%)
cyclosporine	7 (5.0%)
biological treatment (monotherapy or combined)	36 (25.7%)
infliximab	15 (10.7%)
combined with MTX	15
treatment duration, mo	9.2 (8.0) (range 1–28)
etanercept	15 (10.7%)
monotherapy	5
combined with MTX	8
combined with chloroquine	1
combined with azthioprine	1
treatment duration, mo	14.5 (8.9) (range 3–28)
adalimumab	3 (2.1%)
combined with MTX	2
combined with chloroquine	1
treatment duration, mo	2.7 (2.9) (range 1–6)
rituximab	3 (2.1%)
combined with MTX	3
treatment duration, mo	8 (3.5) (range 6–12)

Values are mean (SD) or numbers (percentage)

Abbreviations: DMARD – disease-modifying antirheumatic drug, MTX – methotrexate, others – see TABLE 1

TABLE 3 Significant effects of clinical and laboratory variables on the nutritional status of patients with rheumatoid arthritis (Wilks' λ test)

	Value	F	*P*
TJC	0.88	2.21	0.048
SJC	0.70	7.34	0.000002
M-HAQ	0.69	7.56	0.000001
CRP	0.78	4.67	0.0003
Hb	0.82	3.80	0.002

Abbreviations: SJC – swollen joint count, TJC – tender joint count, others – see TABLE 1

was a nonlinear variable; therefore, the weight was introduced into the analysis to substitute BMI. Then, the analysis of the effect of particular clinical/laboratory variables on individual parameters of the nutritional status was performed. For all tests, *P* value <0.05 was considered statistically significant.

RESULTS **Demographic and clinical characteristics** The most relevant baseline characteristics of patients with RA are presented in TABLE 1.

Most patients were positive for RF-IgM and ACPA and had erosions on radiographs. High disease activity (DAS28 >5.1) was observed in 42 patients (30%). Extra-articular symptoms observed during the course of RA included: rheumatoid nodules in 40 cases, sicca syndrome in 15, interstitial lung disease in 7, renal insufficiency in 2, and vasculitis in 1 patient. At the time of examination, disease-modifying antirheumatic drugs (DMARDs) were not used in 5 patients. In the remaining 135 patients (70.7%), treatment with at least 1 DMARD was administered (TABLE 2). Simultaneously, therapy with biologic response modifiers (biologics) was used in 36 patients (25.7%) (TABLE 2) and low-dose prednisone (≤10 mg/day) in 108 (77.1%).

Some patients presented with concomitant diseases: hypertension (43 [30.7%]), diabetes (6 [4.3%]), coronary heart disease (CHD) (5 [3.6%]), chronic kidney disease (CKD) with glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 (6 [4.3%]). There were no patients with malnutrition syndrome (BMI <20 kg/m^2 and albumin level <3 g/dl).

Effect of clinical/laboratory variables on the nutritional status of RA patients The MANOVA (Wilks' λ test) revealed that the following variables had significant effect on the nutritional status of patients: clinical parameters of RA activity (tender joint count, swollen joint count, M-HAQ), laboratory parameters (CRP, hemoglobin [Hb]) (TABLE 3).

The next step was the analysis of the effect of particular clinical/laboratory variables on individual parameters of the nutritional status (TABLE 4), which allowed to introduce particular formulas of the prognostic nutritional status parameters in RA patients (TABLE 5). Swollen joint count was

TABLE 4 Effect of individual variables on certain parameters of nutritional status in patients with rheumatoid arthritis

	Weight		Albumin		TC		HGS		TSF	
	F	*P*	F	*P*	F	*P*	F	*P*	F	*P*
TJC	0.69	0.4	1.08	0.3	6.22	0.01a	0.36	0.6	0.07	0.8
SJC	0.35	0.66	5.43	0.02[a]	7.94	0.006[a]	6.47	0.01[a]	4.36	0.04[a]
M-HAQ	0.07	0.8	9.24	0.003[a]	0.43	0.5	28.53	0.00001[a]	0.02	0.9
CRP	4.43	0.04[a]	3.20	0.08	14.35	0.0003[a]	2.70	0.1	2.21	0.1
Hb	10.76	0.001[a]	6.45	0.01[a]	0.37	0.5	6.65	0.01a	0.18	0.7

a *P* <0.05 statistically significant

Abbreviations: see TABLES 1 and 3

TABLE 5 Formulas of prognostic nutritional status parameters in patients with rheumatoid arthritis

Variables	R	F	*P*	SE
weight = 24.73 203 + 3.27 587*HB + 0.05 797*CRP	0.34	8.94	0.0002	11.89
albumin = 3.7062 – 0.017 042*SJC – 0.193 947*M-HAQ + 0.067 389*HB	0.52	15.84	0.00000	0.33
total cholesterol = 214.1991 + 2.7612*TJC – 3.0983*SJC – 0.6710*CRP	0.42	9.45	0.00001	41.57
HGS = 15.2781 – 0.7800*SJC – 12.2914*M-HAQ + 2.5368*HB	0.58	21.68	0.00000	14.81
TSF = 19.61 464 – 0.36 865*SJC	0.26	9.08	0.003	6.30

Abbreviations: see TABLES 1 and 4

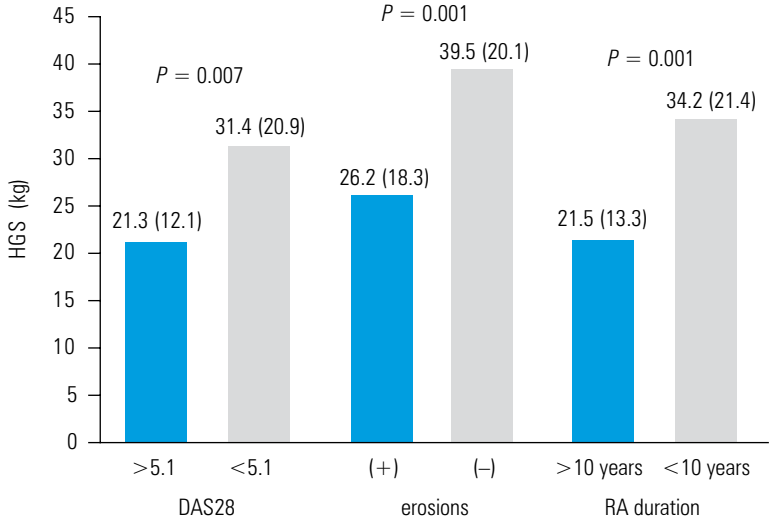

FIGURE 1 Hand-grip strength in patients with high vs. low/moderate disease activity; with vs. without erosions; with long-standing rheumatoid arthritis vs. with rheumatoid arthritis <10 years

Abbreviations: DAS28 – Disease Activity Score, HGS – hand-grip strength, others – see TABLE 1

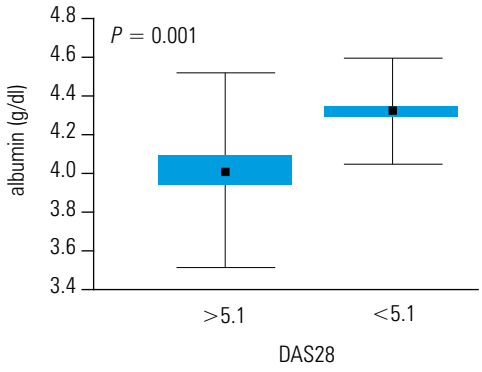

FIGURE 2 Albumin levels in patients with high vs. low/moderate disease activity

associated with a negative effect on several nutritional parameters (serum albumin and TC concentrations, HGS, TSF). M-HAQ was negatively associated with serum albumin and HGS. CRP was negatively connected with TC and positively with weight. Hb was positively associated with weight, serum albumin, and HGS (TABLE 5).

Parameters of nutritional status in patients with high disease activity Patients with high disease activity (DAS28 >5.1), compared with patients with low/moderate RA activity, were characterized by significantly lower HGS (21.3 [12.1] vs. 31.4 [20.9] kg; FIGURE 1) and albumin level (4.0 [0.5] vs. 4.3 [0.3] g/dl; FIGURE 2).

Parameters of nutritional status in patients with erosions and in patients with long-standing rheumatoid arthritis (duration ≥10 years) HGS was lower in patients with erosive RA in comparison with those without erosions (26.2 [18.3] vs. 39.5 [20.1] kg, respectively), as well as in patients with long-standing RA in comparison with RA duration <10 years (21.5 [13.3] vs. 34.2 [21.4] kg, respectively) (FIGURE 1).

A mean TC concentration was higher in patients with erosive RA in comparison with those without erosions (204.3 [45.4] vs. 183.5 [40.7] mg/dl, respectively) as well as in patients with long-standing RA in comparison with RA duration <10 years (210.9 [43.0] vs. 192.5 [45.7] mg/dl, respectively) (FIGURE 3). A higher level of TC in patients with long-standing RA could be also linked with patients' age because there was a correlation between TC and age (R = 0.24, *P* = 0.004).

Parameters of nutritional status in patients treated with biologics We did not find any significant differences between the patients treated with biologics and nontreated patients.

Parameters of nutritional status in patients with concomitant diseases Comparison of patients with vs. without hypertension revealed significant differences in BMI (25.9 [4.4] vs. 24.0 [3.3] kg/m^2, respectively; *P* = 0.005) and total cholesterol. (221.7 [48.1] vs. 191.7 [40.9] mg/dl, respectively; *P* = 0.0002). Patients with diabetes were characterized by significantly higher BMI than those without diabetes (28.2 [4.0] vs. 24.5 [3.7] kg/m^2, respectively; *P*= 0.02). We did not observe any other significant differences; however, the number of patients with diabetes, CHD, and CKD was quite low.

DISCUSSION The results of this study indicate that in patients with RA, the parameters of nutritional status are associated with both inflammatory and clinical markers of the disease activity. The nutritional parameters were significantly correlated with the markers of inflammatory disease activity (swollen and tender joint counts, CRP, Hb) and physical disability (M-HAQ). When

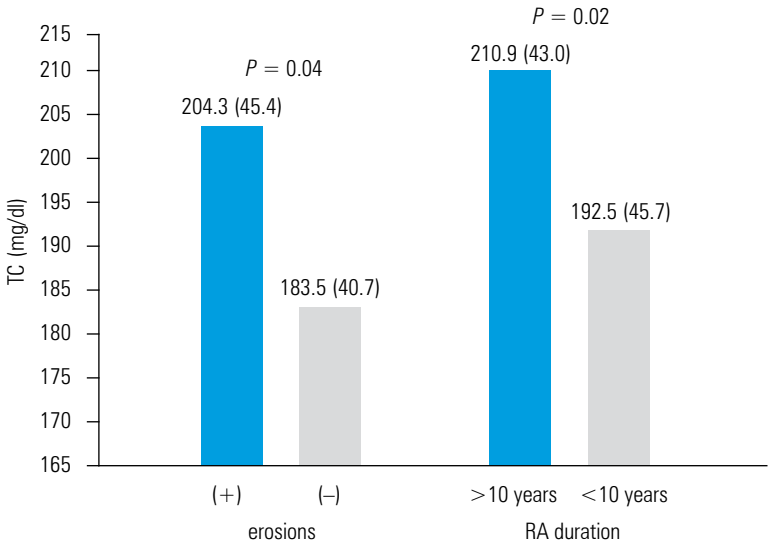

FIGURE 3 Total cholesterol levels in patients with vs. without erosions; with long-standing rheumatoid arthritis vs. with rheumatoid arthritis <10 years
Abbreviations: TC – total cholesterol, others – see **FIGURE 1**

assessing individual parameters, swollen joint count was negatively related to several parameters of nutritional status as well as M-HAQ. Hb was positively correlated with nutritional parameters. In patients with high disease activity (DAS28 >5.1) significantly lower HGS and albumin levels were noted. Advanced stages of the disease (erosive form and/or long-standing RA) were characterized by significantly lower HGS values and higher TC concentrations. Higher TC levels in these patients could also be associated with age and hypertension, suggesting increased cardiovascular risk.

In our study, the 5 chosen parameters (anthropometric and biochemical) represented the nutritional status of patients. These parameters may be assessed quite easily in every patient with RA.

BMI is a simple and generally used index for evaluation of nutrition. In literature, cross-sectional comparisons of patients with RA and healthy controls showed no significant difference in BMI.[9-10] However, low body weight has been associated with more active disease and greater level of disability.[2-3] Low BMI has also been reported as an independent predictor of poor radiological outcome, more useful for this purpose than the presence of shared epitope, erosions at baseline, or extra-articular features.[11] However, adipose tissue, particularly visceral fat, is the source of CRP, and it may contribute to the serum CRP levels of RA patients independently of their disease activity.[12] In our study, we found a positive association between CRP and weight.

The quantity of visceral protein is expressed by serum albumin. Hypoalbuminemia has traditionally been considered a classic condition of RA patients, not secondary to undernutrition.[10] Inflammation can cause hypoalbuminemia by suppressing albumin synthesis and by causing transfer of albumin from the vascular to the extravascular space.[13] Patients with RA also have increased whole-body protein breakdown, and higher TNF-α production is associated with higher rates of protein catabolism.[14] It was reported that in RA patients serum albumin was lower than in controls and was statistically associated with RA functional class.[10] In our study, serum albumin was negatively correlated with clinical, functional, and laboratory markers of disease activity.

HGS shows skeletal muscle strength. It has been reported to be a good marker of nutritional status in surgical patients and patients with chronic renal failure.[15] Additionally, in RA patients the skeletal muscle strength, especially of the hands, is impaired due to disease activity and joint pain. In our study, HGS was negatively associated with swollen joint count and M-HAQ, and positively associated with Hb.

TSF provides information exclusively about fat mass and is potentially less affected by RA.[10] Gómez-Vaquero et al.[10] observed no significant differences in TSF between RA patients and controls; however, TSF was different in patients with RA functional class IV. In our study, TSF was negatively associated with swollen joint count.

Lipid content in the blood is reflected by serum TC. Inflammation appears to be inversely associated with cholesterol levels. In severe, untreated RA, reductions in HDL-cholesterol, LDL-cholesterol, and TC have been noted.[16] In our study, TC was negatively associated with swollen join count and CRP.

Cachexia is often seen in diseases with chronic inflammatory response, such as cancer, acquired immune deficiency syndrome, cardiac failure, and tuberculosis.[1,2,17] It manifests with excessive weight loss, low muscle mass with low fat mass, and is always associated with poor prognosis.[3,4] Rheumatoid cachexia is different because it is associated with normal or increased fat mass and BMI, with concurrent loss of body protein that predominates in skeletal muscle mass, but also occurs in other tissues and the immune system as a component of BCM.[3,4] Therefore, it can be undetected in routine clinical practice due to normal or increased weight or BMI of patients. The consequence is not only muscle weakness but also impaired adaptation to metabolic stress, affecting increased mortality and morbidity.[2,4]

A number of factors are involved in the pathogenesis of rheumatoid cachexia including proinflammatory cytokines (mainly TNF-α, IL-1β, IL-6), excessive energy expenditure, high rates of whole-body protein breakdown, loss of muscle mass and strength, reduced physical activity due to joint pain and stiffness.[1,14] It was demonstrated that rheumatoid cachexia could not be related to diet fat intake; therefore, it could not be cured only by dietary intervention.[17] Other studies reported significant correlations between depletion of BCM and increased number of swollen joints, ESR, CRP, DAS28, and IL-6 levels.[3,4] Simultaneously, it was shown that these meta-

bolic changes were associated with risk factors of cardiovascular disease.[9,18] In the general population, obesity is an established risk factor for CHD and mortality. In contrast, RA patients with higher BMI have lower mortality rate than thinner patients.[19] In patients with RA, low BMI is an important predictor of increased cardiovascular mortality.[9]

It is estimated that RA patients have a mean of ~15% less BCM than matched healthy controls with a dose-response relationship with RA severity.[5,10] Decrease of BCM in RA is thought to accelerate during times with the highest production of proinflammatory cytokines. That is why anticytokine therapy, especially anti-TNF-α treatment, could be a means of restoring BCM in RA patients.[5] However, the available reports have presented only short-term, preliminary data.[20,21] According to the EULAR recommendations, the treatment should be adapted to an individual patient and the current activity of the disease, with intensive strategies in patients with poor prognosis.[22]

Parameters of nutritional status presented in our study can be easily measured and may be helpful in estimating the patient's general condition. Our study showed that the nutritional status of RA patients was determined by an intensity of chronic inflammatory process continuing in the course of disease and by disease duration.

Acknowledgements We would like to thank Professor Andrzej Krajka (Maria Curie-Skłodowska University of Lublin) for his help with statistical data analysis.

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ARTYKUŁ ORYGINALNY

Zależności między wskaźnikami stanu odżywienia i aktywności choroby wśród chorych na reumatoidalne zapalenie stawów

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SŁOWA KLUCZOWE

aktywność choroby, kacheksja reumatoidalna, reumatoidalne zapalenie stawów, rokowanie, stan odżywienia

STRESZCZENIE

WPROWADZENIE Wśród chorych na reumatoidalne zapalenie stawów (RZS) obserwuje się zmniejszenie komórkowej masy ciała, określane mianem kacheksji reumatoidalnej. Kacheksja wiąże się ze zwiększoną chorobowością i przedwczesną umieralnością tych chorych.

CELE Celem pracy była ocena wpływu przewlekłego procesu zapalnego i aktywności choroby na stan odżywienia chorych na RZS.

PACJENCI I METODY W grupie 140 chorych (111 kobiet, 29 mężczyzn) określono aktywność RZS z wykorzystaniem wskaźnika aktywności choroby ocenianego w 28 stawach (Disease Activity Score – DAS28) i zmodyfikowanego kwestionariusza jakości życia (Modified Health Assessment Questionnaire – M-HAQ). Stan odżywienia oceniano za pomocą następujących parametrów: stężenia albuminy i cholesterolu całkowitego (*total cholesterol* – TC) w surowicy, wskaźnika masy ciała, siły zacisku rąk oraz grubości fałdu skórnego nad mięśniem trójgłowym.

WYNIKI Wykazano istotny związek między parametrami stanu odżywienia a wskaźnikami zapalnymi aktywności choroby (liczbą stawów obrzękniętych i bolesnych, białkiem C-reaktywnym, hemoglobiną) oraz niewydolności fizycznej (M-HAQ). Liczba stawów obrzękniętych i M-HAQ wykazywały ujemną korelację z kilkoma parametrami stanu odżywienia. U chorych z dużą aktywnością RZS obserwowano istotnie mniejszą siłę zacisku rąk oraz istotnie mniejsze stężenie albuminy. Zaawansowane postacie RZS (nadżerkowa i/lub długotrwała) były związane z mniejszą siłą zacisku rąk i większym stężeniem TC.

WNIOSKI Stan odżywienia chorych na RZS jest zdeterminowany nasileniem przewlekłego procesu zapalnego towarzyszącego chorobie i czasem jej trwania.

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Praca wpłynęła: 16.12.2010.
Przyjęta do druku: 29.03.2011.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2011; 121 (4): 122-128