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ORIGINAL ARTICLE

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Malnutrition and disease progression in patients with rheumatoid arthritis

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Abstract To examine the changes in nutritional status during the progression of rheumatoid arthritis (RA), we studied anthropometric and biochemical variables in 97 Japanese patients with RA. Anthropometric data included body mass index (BMI), triceps skinfold thickness (TSF), and arm muscle area (AMA). Levels of albumin and cholesterol in serum, and lymphocyte count were studied as biochemical variables. The prevalence of malnutrition defined as hypoalbuminemia less than 3.4 g/dl was 24.7%, similar to the reports in other countries. Analysis of the data according to disease stage showed that malnutrition in RA was characterized by a progressive reduction in body protein. Body mass index and TSF were increased in patients with stage 1 disease, whereas serum albumin and AMA were within normal range. Stage 2 patients had normal BMI with decreased body protein, albumin, and AMA. Progression to stages 3 and 4 was associated with a stepwise decrease in AMA; serum albumin and BMI remained in the same range as stage 2. Albumin values and AMA were significantly lower in patients with poor functional class and high C-reactive protein. The characteristic progression of malnutrition in RA is attributed to excessive protein catabolism evoked by inflammatory cytokines and by disuse atrophy due to functional impairment.

Key words Anthropometry · Cytokine · Functional disability · Nutrition · Rheumatoid arthritis (RA)

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Introduction

Malnutrition is more common in patients with rheumatoid arthritis (RA) than in healthy individuals,[1–5] but reports on malnutrition associated with RA are very rare in Asian countries. Even in Western countries, the relation between nutritional status and progression of RA remains poorly understood. We examined whether the nutritional status of Japanese patients with RA is related to disease activity and progression.

Materials and methods

Ninety-seven patients with RA were studied. They were all regularly attending an outpatient clinic at Kyoto Second Red Cross Hospital or the Department of Rheumatology, Kyoto Prefectural University of Medicine. All patients had a diagnosis of RA according to the American Rheumatism Association criteria (ARA) of 1987.[6]

Nutritional status was assessed by measuring anthropometric and biochemical variables. Anthropometric variables included height (H), weight (W), mid-upper-arm circumference (AC), and triceps skinfold thickness (TSF). Triceps skinfold thickness was measured at the mid-point between the acromion process and the tip of olecranon with a Harpenden caliper. Mid-upper-arm circumference measurement was taken at the same level with insertion tape. From these measurements, body-mass index (BMI) and arm muscle area (AMA) were calculated as follows[7]:

$$\mathrm{BMI} = \mathrm{W\ (kg)/H\ (m)^2}$$
$$\mathrm{AMA} = [(\mathrm{AC\ (cm)} - \pi\mathrm{TSF\ (cm)}]^2/4\pi$$

For comparative study, percentage of AMA (%AMA) and TSF (%TSF) to age- and sex-adjusted mean values, which were obtained from Japanese Anthropometric Reference Data,[8] were used.

Nutritional status was evaluated on the basis of serum albumin level, total cholesterol level, and lymphocyte

count. As control, 81 healthy volunteers of comparable age and sex were studied. Body mass index and biochemical variables were compared between the patients with RA and controls. These variables were studied according to the stage of RA,[9] class of functional disability,[10] and disease activity, evaluated on the basis of C-reactive protein (CRP) level, rheumatoid factor (RF) titer, and whether or not patients were receiving corticosteroids. Student's *t*-test was used to calculate the statistical significance of differences between the patients and control.

Results

The demographic and clinical characteristics of the patients are shown in Table 1. The BMI of the patients was similar to that of the control subjects and approximated the ideal value. The levels of albumin and total cholesterol in serum and the lymphocyte count were significantly lower in patients with RA than in control (Fig. 1). The serum albumin value was less than 3.4 g/dl in 24.7% of the patients, as compared with only 1.0% of the controls. As for anthropometric measurements, %AMA was less than 80 in 28.8% of the patients, while BMI was below 18 in only 11.6% (Table 2).

Nutritional status was compared among the four stages of RA. In patients with stage 1 disease, BMI, 24.12, was significantly increased compared with controls, 22.29 ($P = 0.017$), whereas albumin level and AMA were within the normal range. Triceps skinfold thickness (126% of normal) was also increased in the stage 1 group. Stage 2 patients had a normal BMI, with decreased visceral protein, albumin, and AMA. In stages 3 and 4, AMA, representing muscle protein, decreased in a stepwise fashion (82.4% and 74%, respectively), whereas serum albumin and BMI remained in the same range as stage 2 (Fig. 2).

Table 1. Demographic data

	RA patients	Controls
Number	97	81
Male	20	19
Female	77	62
Age (years)	29–79	27–73
(Mean ± SD)	(61.77 ± 11.13)	(55.78 ± 10.6)
Stage 1	22	
Stage 2	27	
Stage 3	33	
Stage 4	15	

RA, rheumatoid arthritis

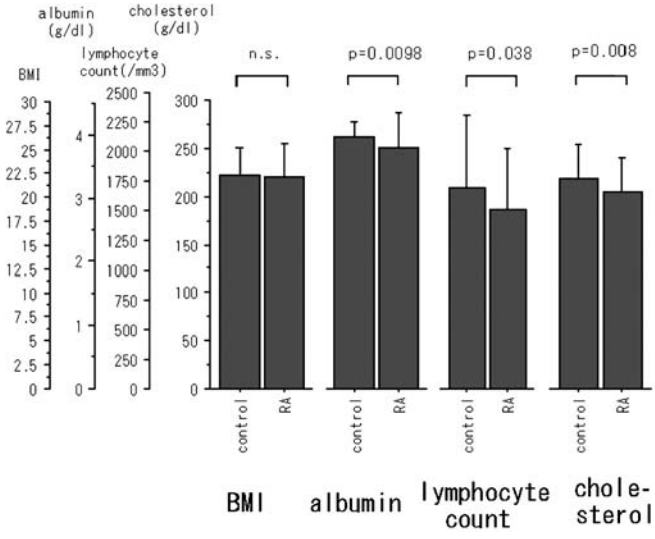

Fig. 1. Comparison of nutritional variables between patients with rheumatoid arthritis (*RA*) and control subjects. Serum albumin level, total cholesterol level, and lymphocyte count were significantly lower in the patients than in control. Body mass index (*BMI*) was similar

Table 2. Distribution of the patients according to body mass index (BMI), serum albumin, and percent arm muscle area (%AMA)

(A) Body mass index	<18	18–20	20–22	22–24	>24
Control (%)	5 (6.2)	15 (18.5)	19 (23.5)	20 (24.7)	22 (27.2)
RA (%)	11 (11.3)	18 (18.6)	22 (22.7)	19 (19.6)	27 (27.8)
(B) Serum albumin (g/dl)	<3.0	3.0–3.4	3.4–3.8	3.8–4.2	>4.2
Control (%)	0 (0)	1 (1.2)	15 (18.5)	49 (60.5)	16 (19.8)
RA (%)	4 (4.1)	20 (20.6)	21 (21.6)	27 (27.8)	25 (25.8)
(C) %AMA	<60	60–80	80–100	100–120	>120
RA (%)	7 (7.2)	21 (21.6)	38 (39.2)	22 (22.7)	9 (9.3)

The prevalence of malnutrition, as defined by a BMI of <18, a serum albumin level of <3.4 g/dl, and a %AMA of <80 was 11.3%, 24.7%, and 28.8%, respectively

The results of comparative analysis according to functional class were very similar to those of analysis according to disease stage. Body mass index, albumin, and AMA were significantly lower in the patients with class 2 and higher disability than the patients with class 1 disability. We compared the mean values of the nutritional variables between the following groups: patients in whom CRP was positive versus those in whom CRP was negative; patients with a high RF titer (>50) versus those with a low RF titer; and patients who were receiving corticosteroids versus those who were not. Serum albumin level and %AMA were significantly lower in the patients in whom CRP was positive than in those in whom CRP was negative. None of the nutritional variables differed significantly between patients with a high RF titer versus those with a low RF titer, or between patients who were receiving corticosteroids and those who were not (Table 3).

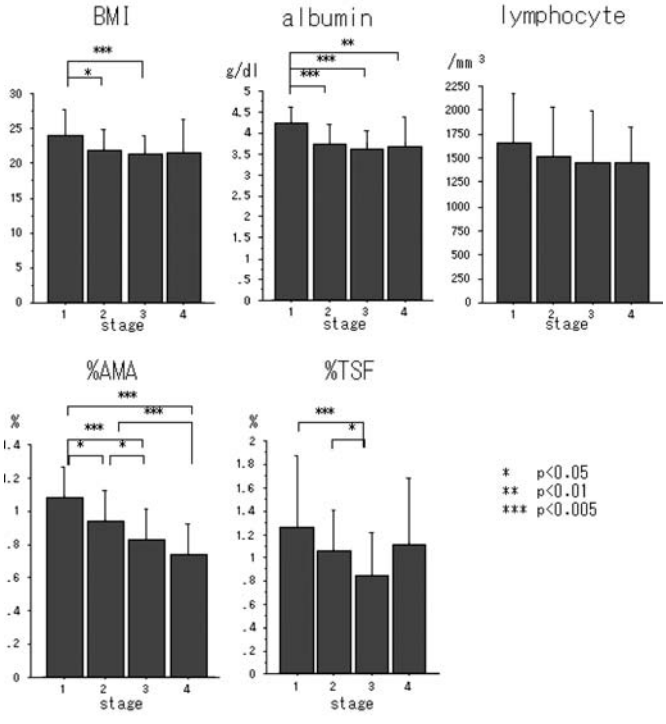

Fig. 2. Comparative analysis of nutritional status of patients according to stage of rheumatoid arthritis (RA). The mean values of *BMI*, serum *albumin*, and *lymphocyte* count in healthy controls were 22.29, 3.98 g/dl, and 1697/mm^3, respectively. In patients with stage 1 RA, BMI was significantly increased compared with control, and albumin level and arm muscle area (*AMA*) were within the normal range. Body mass index and serum albumin levels were significantly lower in the patients with advanced disease than in those with stage 1 disease. %AMA decreased in a stepwise fashion with the progression of disease. *TSF*, triceps skinfold thickness

Discussion

Malnutrition occurs in 23.2%–50% of patients with RA,[1,5] often in association with reduction of rapid turnover proteins such as transferrin and prealbumin and reduced lean body mass.[1,2] We believe that our study was one of the first to assess malnutrition in Japanese patients with RA and to explore the relation between nutritional status and disease progression.

Malnutrition as defined by hypoalbuminemia was seen in 24.7% of patients with RA. This prevalence is similar to that reported previously in Western countries, suggesting that differences in genetic backgrounds and social conditions do not affect nutritional status in patients with RA.

Malnutrition in our patients was characterized by a progressive reduction in body protein. Obesity associated with increased fat depots, as reflected by the TSF values, without a decrease in protein, was common in stage 1, early RA. Disease progression led to decreased levels of visceral and muscle proteins, represented by serum albumin and AMA; BMI became normal in stage 2. In stages 3 and 4, muscle protein decreased further, whereas albumin, i.e., visceral protein, did not change significantly. Mean BMI in the advanced stages of RA appeared to remain in the ideal range, since subcutaneous fat increased to compensate for the decline in protein.

The characteristic progression of malnutrition in RA should be attributed to excessive protein catabolism evoked by inflammatory cytokines and by disuse atrophy due to functional impairment. Cytokines, i.e., tumor necrosis factor α (TNFα), interleukin 1β (IL-1β), and interferon-γ, mediators of inflammation in RA,[11] are known to regulate fat, carbohydrate, and protein metabolism.[12] Roubenoff et al. reported a direct association between production of

Table 3. Alterations in BMI, serum albumin, and AMA according to disease activity of RA

		No.	BMI	Albumin	Lymphocytes (/μl)	%AMA
Functional class	1	31	23.3 ± 3.56	4.17 ± 0.42	1650 ± 507	104.2 ± 17.4
	2	49	21.3 ± 2.84**	3.59 ± 0.42**	1448 ± 517	85.2 ± 20.8**
	3	17	22.1 ± 4.34	3.78 ± 0.67*	1466 ± 365	77.6 ± 19.4**
CRP	<0.5	45	22.2 ± 3.29	4.01 ± 0.50	1508 ± 396	96.1 ± 19.5
	≥0.5	52	22.0 ± 3.65	3.63 ± 0.50***	1524 ± 575	84.7 ± 22.6***
RF	<50	44	22.1 ± 3.08	3.83 ± 0.47	1477 ± 505	94.6 ± 20.2
	≥50	53	22.1 ± 3.79	3.78 ± 0.58	1552 ± 494	86.1 ± 22.6
Steroid medication	(−)	41	21.9 ± 3.60	3.92 ± 0.50	1594 ± 413	90.6 ± 20.0
	(+)	56	22.3 ± 3.39	3.72 ± 0.55	1458 ± 550	89.5 ± 24.0

CRP, C-reactive protein; RF, rheumatoid factor
*$P < 0.05$ vs class 1, **$P < 0.01$ vs class 1, ***$P < 0.01$ vs (CRP < 0.5)

cytokines, TNFα and IL-1β, and resting energy expenditure in patients with RA. They revived the term "rheumatoid cachexia" to describe malnutrition in RA, caused by cytokine-driven hypermetabolism.[3] In this study, the decreases in visceral and muscular proteins were more remarkable in patients with active disease and high CRP levels. Because the production of IL-1β and other cytokines are known to correlate with disease activity in RA,[13,14] this result shows that inflammatory cytokines are playing an important role in pathogenesis of malnutrition in RA.

It is very plausible that functional impairment causes disuse muscle atrophy, accelerating the catabolism of muscle proteins. This mechanism is supported by our findings that muscle protein decreased with advancing functional class. Do changes in oral intake play some role in the changes in nutritional status associated with RA? Previous reports describe the dietary intake of energy, carbohydrates, vegetable proteins, and lipids as not being lower in patients with RA than in healthy controls.[3,4] Our finding that BMI in patients with advanced RA continues to approximate the ideal range suggests that energy intake in these patients is not decreased.

We have no clinical evidence indicating that poor nutritional status worsens prognosis in patients with RA. However, decreased levels of visceral proteins are likely to have negative physiological effects on the cardiovascular and immune systems, while reductions in muscle protein accelerate functional impairment. Therefore, prevention of malnutrition, mainly involving abnormalities of body composition, seems to have a very important role in the total care of patients with RA. From a nutritional perspective, our results suggest the following two conclusions. (1) Malnutrition in patients with RA involves progressive decreases in visceral and muscle proteins caused by activation of inflammatory cytokines and disuse atrophy. Control of disease activity and adequate exercise are therefore essential for prevention. (2) As dietary nutritional support, which is much less important than control of disease activity, in RA, a high-protein diet may be recommended for the patients at an advanced disease stage and decreased visceral protein. Restriction of excessive carbohydrate intake to prevent obesity may also be beneficial in patients with early RA.

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