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Nutritional status in patients with rheumatoid arthritis

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SUMMARY A nutritional assessment of 50 patients with rheumatoid arthritis (RA) showed evidence of malnutrition in 13 (26%), while all 50 control subjects had normal nutritional status. Of the anthropometric measurements the body-mass index and triceps skinfold thickness values in men and women were significantly reduced in RA patients compared with controls. Upper arm muscle circumference was significantly less in male but not female rheumatoid patients. In addition all six biochemical determinants of nutrition assayed–serum albumin, transferrin, retinol-binding protein, thyroxine-binding prealbumin, zinc, and folic acid–were significantly lower in the RA group of patients. Malnourished patients had more active disease than the remaining RA patients, with significantly higher ESR, C-reactive protein, and α_1 antichymotrypsin measurements. Significant inverse correlations were found between some biochemical measurements of nutrition and indices of disease activity. Our results suggest that in RA the severity of disease adversely affects the nutritional status.

It is well recognised that disease processes can interfere with adequate nutrition and even lead to a malnourished state. While much attention has been given to surgical conditions, gastrointestinal disease, and cancer, there are few data on patients with inflammatory joint disease.

Deficiencies of several nutritional factors have been shown to occur in rheumatoid arthritis (RA) and include folic acid,[1] vitamin D,[2] and zinc deficiency.[3 4] Furthermore retinol-binding protein (RBP) and thyroxine-binding prealbumin (TBPA), both sensitive indicators of protein-energy malnutrition,[5] have been found to be reduced in RA patients compared with controls.[6 7]

Despite these findings there has been no comprehensive study concerning the nutritional status in patients with RA. Our aim, therefore, was to assess whether malnutrition is an associated feature of RA and, if present, to determine its cause.

Patients and methods

Patients. Fifty out-patients with RA (30 female, 20 male) were studied. Thirty-eight (76%) were seropositive for rheumatoid factor and all satisfied the American Rheumatism Association criteria for classical or definite RA. The average disease duration was 6·9 years and the age range was 27 to 80 years (mean 59·7 years). All but six patients were taking either aspirin preparations or nonsteroidal anti-inflammatory drugs (NSAIDs); additional treatments included sodium aurothiomalate (11 patients), prednisolone (9), D-penicillamine (5), and azathioprine (2).

Controls. As a control group an equal number of male and female outpatients with non-inflammatory musculoskeletal conditions (mainly degenerative joint disease or mechanical low back pain) were also studied. Their age range was similar to that of the rheumatoid patients (22 to 83 years) with a mean of 59·2 years.

Evaluation of disease activity. Disease activity in RA patients was assessed clinically by the number of painful joints, the duration of early morning stiffness (in minutes), the mean grip strength values (in mmHg), and biochemically by the erythrocyte sedimentation rate (ESR, Westergren method), C-reactive protein (CRP), and α_1 antichymotrypsin (α_1ACT) measurements.

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Nutritional assessment. All 100 patients had a nutritional assessment based on standard methods.[8-10] Anthropometric measurements included height, weight, and mid upper arm circumference. Triceps skinfold thickness (TSF) was measured at the midpoint between the acromion and olecranon process with a Harpenden calliper. From these measurements the body-mass index (BMI)[11] and upper arm muscle circumference (UAMC) were calculated and the percentages of ideal values were obtained. A reduction below 80% of ideal weight for height and values of less than 80% and 60% for UAMC and TSF respectively indicated a significant deficit.

Four visceral proteins–serum albumin, transferrin, RBP, and TBPA–were used as biochemical determinants of the nutritional status. In addition, serum levels of zinc and folic acid were measured. Measurements were made without any accompanying clinical or anthropometric information.

Patients were judged to be malnourished if they had a reduction of at least one anthropometric measurement in conjunction with two or more biochemical abnormalities.

Biochemical methods. The serum concentrations of α_1ACT, TBPA, and RBP were measured by 'Rocket' immunoelectrophoresis.[12] The assay conditions for TBPA and RBP have been described previously.[13] Rocket immunoelectrophoresis of α_1ACT was accomplished with a gel antibody (Dakoimmunostics No. AO22) concentration of 0·95%. A voltage gradient of 11 V/cm across the gel was used with a four-hour running time. Calibration of the α_1ACT assay was achieved with a human plasma protein standard (Behringwerke AG).

The concentration of CRP was measured by radial immunodiffusion and transferrin by laser nephelometry (Hyland Laser nephelometer) with assay conditions as described in methods for quantitation of human serum proteins using Immunostics antisera (Seward Laboratory, UAC House, Blackfriars Road, London). An automated bromocresol green method[14] was used for the assay of serum albumin. Serum zinc was measured by atomic absorption spectrophotometry (Instrumentation Laboratory 155 atomic absorption spectrophotometer) at a wavelength of 213·9 nm.

Statistical analysis. Student's *t* test was used to calculate any statistical significance between data in the different patient groups. A rank correlation matrix was constructed to evaluate any significant interrelationship of up to eight biochemical variables. All calculations were made on a CBM Model 8050 computer.

Results

With the exception of UAMC in female patients, significantly lower values of all anthropometric measurements were found in RA patients compared with control subjects (Table 1). Surprisingly for a condition in which muscle wasting is often a prominent feature, a significant reduction in UAMC was present in only 14% of RA patients, whereas weight and TSF deficits occurred twice as frequently. The biochemical indices of nutrition are shown in Table 2; all values were significantly lower in the rheumatoid group of patients.

Thirteen RA patients fulfilled the criteria of malnutrition, and five were severely affected with major abnormalities on both anthropometric and biochemical testing. By contrast, none of the control subjects were judged to be malnourished although occasional anthropometric abnormalities were found and three had low folic acid levels.

In order to determine the possible causes of impaired nutrition we examined various factors that might influence the nutritional status. A detailed dietary assessment was carried out on the first 25 consecutive RA patients entered into the study.

Table 1 *Comparison of anthropometric measurements in RA patients and controls*

	RA patients (n=50)			*Controls (n=50)*			
	Mean	*SD*		*Mean*	*SD*		*p value*
Body-mass index (W/H^2)*	22·7	3·6	(30%)	25·5	3·3	(4%)	<0·001
Triceps skinfold thickness (mm)							
female	15·7	6·6	(28%)	21·2	6·6	(4%)	<0·01
male	8·9	3·2		12·7	3·3		<0·001
Upper arm muscle circumference (cm)							
female	21·8	3·5	(14%)	22·0	2·0	(4%)	NS
male	23·6	2·7		26·0	2·4		<0·01

*W=weight in kg, H=height in m.
Values in parentheses indicate the percentage of patients with significant deficits. NS=not significant.

Table 2 *Comparison of biochemical indices of nutrition in RA patients and controls*

	RA patients (n=50)		*Controls (n=50)*		
	Mean	*SD*	*Mean*	*SD*	*p value*
Albumin (g/l)	39·3	4·1 (14%)	43·5	3·1 (—)	<0·001
Transferrin (g/l)	2·8	0·5 (18%)	3·3	0·6 (—)	<0·001
Zinc (μmol/l)	12·3	2·3 (8%)	13·5	2·2 (—)	<0·05
Retinol-binding protein (mg/l)	53·7	18·9 (26%)	68·2	13·9 (—)	<0·001
Thyroxine-binding prealbumin (g/l)	0·21	0·09 (24%)	0·27	0·07 (—)	<0·001
Folic acid (μg/l)	3·2	1·5 (20%)	3·8	1·6 (6%)	<0·05

Values in parentheses indicate the percentage of patients with measurements below the laboratory reference range.

However, since all these patients, including six with overt malnutrition, were considered to have had a satisfactory dietary intake, we discontinued this form of evaluation on subsequent patients.

Malnourished patients could not be distinguished from the remaining RA patients by either a difference in their age or duration of disease (Table 3). However, on clinical evaluation, the majority of malnourished patients had severe RA, and 10 of the 13 had ESR values of greater than 50 mm/h. In keeping with the clinical assessment all three indices of inflammation the ESR, CRP, and α_1ACT were significantly increased in the malnourished group (Table 3).

A rank correlation matrix was constructed to determine any significant interrelationships among the biochemical indices of nutrition and also the acute-phase proteins α_1ACT, and CRP (Table 4). As expected, the most significant correlations existed between RBP and TBPA ($r=0·87$, $p<0·001$) and α_1ACT and CRP ($r=0·63$, $p<0·001$). Significant correlations were also found between the serum albumin

Table 3 *Comparison of age, disease duration, and indices of inflammation in malnourished patients (n=13) and the remaining rheumatoid patients (n=37)*

	RA patients (n=50)				
	Malnourished (n=13)		*Remainder (n=37)*		
	Mean	*SD*	*Mean*	*SD*	*p value*
Age (years)	59·7	10·9	59·4	12·4	NS
Disease duration (years)	9·9	8·7	6·7	7·5	NS
Disease activity					
ESR (mm/h)	63·2	25·1	34·4	16·4	<0·001
CRP (mg/l)	99·3	63·6	40·6	41·2	<0·01
α_1ACT (g/l)	1·96	0·77	1·30	0·73	<0·05

Table 4 *Computer-constructed rank correlation matrix for the biochemical determinants of nutrition and the acute-phase reactants, CRP and α_1 ACT. Values represent rank correlation coefficients*

	Folate	*α_1ACT*	*RBP*	*TBPA*	*CRP*	*Albumin*	*Zinc*
Transferrin	0·1	−0·17	0·21	0·1	−0·21	0·36*	0·23
Zinc	0·17	−0·38**	0·1	0·11	−0·13	0·37**	
Albumin	0·24	−0·27	0·42**	0·33*	−0·21		
CRP	−0·25	0·63***	−0·53***	−0·54***			
TBPA	−0·06	−0·45**	0·87***				
RBP	−0·08	−0·43**					
α_1ACT	−0·05						

*p<0·05. **p<0·01. ***p<0·001.

and the following; transferrin, zinc, RBP, and TBPA. Serum folate showed no significant correlation with any other biochemical index of nutrition.

The apparent relationship between disease activity and nutritional impairment was further observed by finding significant negative correlations between both acute-phase proteins and RBP and TBPA.

Discussion

There is no single definitive test of nutritional status, and the diagnosis of malnutrition requires a profile that includes a dietary history, anthropometric evaluation, and biochemical and immunological tests. We found a dietary assessment unhelpful, since it appeared not to distinguish malnourished patients from the remainder. We also omitted the use of skin tests in assessing nutritional status because previous studies have shown that RA patients have impaired delayed cutaneous hypersensitivity.[15-17]

Even with the use of multiple objective anthropometric and biochemical measurements a precise diagnosis of malnutrition is difficult to arrive at. However, our criteria, which relied on a combination of abnormal anthropometric and biochemical tests, are more stringent than those used by other investigators.[18]

We have shown that an impaired nutritional state may be present in some patients with RA, especially those with severe disease. Recently Richter and his colleagues have suggested that TBPA may be a sensitive indicator of disease activity, since they demonstrated significantly depressed levels in active RA and an inverse correlation with CRP.[7] In our study a significant negative correlation was also found between TBPA and CRP, implying that, in isolation, TBPA may act as a negative acute phase protein. However, of the 12 patients with depressed TBPA levels all but two had other nutritional abnormalities, and we thus believe that in RA the severity of disease adversely influences the nutritional state with a consequent depression in the visceral protein mass. Low RBP levels have been previously reported in RA patients, and it has been suggested that zinc deficiency may be a causative factor.[6] Our data do not support this hypothesis, as we were unable to show any relationship between zinc and RBP. Nevertheless we would agree that reduced RBP may have some diagnostic value in distinguishing between RA and osteoarthritis.

Several studies have shown that zinc levels are reduced in RA.[3,4] Our results support previous work by Balogh *et al.*,[4] who demonstrated a significant correlation between zinc and albumin levels and an inverse relationship with ESR measurements. While we did not include the ESR in the correlation matrix, a significant negative correlation was found between zinc and α_1ACT, another index of inflammation.

It is thought that in chronic inflammatory disorders zinc levels are influenced by leucocyte endogenous mediator (LEM), which promotes the hepatic sequestration of both iron and zinc.[19] In addition LEM stimulates the hepatic production of acute-phase proteins and affects the nutritional status, mainly by the acceleration of skeletal muscle proteolysis.[20] LEM is released by macrophages in the presence of tissue damage and complement activation, and in view of the relationship that we have demonstrated between malnutrition and active disease it is not unreasonable to speculate that this mechanism may also occur in RA. Alternatively it is possible that the increased synovial proliferation in the joints of RA patients may place an increased demand on certain nutrients, such as folic acid.[1]

Whatever the mechanism, it may be relevant that some of the consequences of malnutrition, such as impaired delayed cutaneous hypersensitivity, an increased susceptibility to infection, poor skin integrity, and anaemia, are all recognised complications of RA. The appreciation of malnutrition in RA may therefore have clinical implications.

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Book review

Fine Structure of Synovial Joints. By Feroze N. Ghadially. Pp. 333. £45·00. Butterworths: London. 1983.

Professor Ghadially is well known for previous contributions on ultrastructural appearances, including those of joints. This new book is well produced and generously endowed with high quality photographs, as befit the subject matter. The first four chapters take us through the appearances of normal synovial membrane, articular cartilage, the articular surface, and discs and menisci. The remaining 10 chapters describe the changes in traumatic arthritis, haemophilia and haemarthrosis, villonodular synovitis, rheumatoid and osteoarthritis, ganglia, and some lesions produced experimentally in animals. Ultrastructural studies, including analytical electron microscopy, have an important role to play in the diagnosis and study of crystal-induced joint disease, and it is regretted that this aspect of joint disease has been omitted completely from the book.

Each chapter is well set out and includes a historical and introductory section together with descriptions of naked eye and light microscopical appearances which successfully combine to put the electron microscopy in context. Furthermore the implications of the ultrastructural features are discussed for each topic. There are occasional inaccuracies in the citation of references, but the bibliography for each chapter is good. The author has set out to provide sufficient background to the ultrastructural appearances for the non-specialist to understand the text and likewise enough pathological detail for the non-clinical worker. This is mainly by the use of footnotes and cross-references to a previous more general book by the same author. The approach worked well for the reviewer.

This is a thoughtfully prepared book which is easily read. It must find an important place in the libraries of those interested in the pathology of joints.

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