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ORIGINAL ARTICLE

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The effect of disease activity on fat-free mass and resting energy expenditure in patients with rheumatoid arthritis versus noninflammatory arthropathies/soft tissue rheumatism

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Abstract Rheumatoid arthritis (RA) is a chronic joint disease of undetermined cause that is associated with significant disability. Low-grade fever, anemia, and weight loss are recognized extra-articular features associated with increased disease activity. Weight loss and cachexia are well-established features of RA. The mechanism behind weight loss in RA is not known and may be multifactorial. Reduced energy intake and hypermetabolism are the major two factors frequently implicated in the etiology of RA cachexia. One would expect the effect of the above two factors to be highest during increased disease activity and lowest during remission. The purpose of this study was: (a) to establish whether in RA patients changes in body composition mirror changes in disease activity, (b) to investigate the relation between the energy expenditures and weight loss, (c) to examine the dietary energy intake and its role in weight loss in RA patients, and (d) to investigate the relation between the cytokine interleukin (IL)-6 and other variables including resting energy expenditure (REE), body composition, and acute phase reactants. Fourteen patients with RA were age-, sex-, and race-matched with 14 controls from patients with noninflammatory diseases/soft tissue rheumatism. The measurements included the following: disease activity assessment, anthropometric measurements, indirect calorimetry, and measurements of dietary intake. Blood was collected to measure the acute-phase reactants and IL-6 levels. We demonstrated that loss of fat-free mass (FFM) might accelerate during times of increased disease activity and is only partially restored during periods of reduced disease activity. This probably means that the extent of cachexia in RA patients is determined by the frequency and intensity of disease activity (flare) for a given disease duration. Hypermetabolism with increased REE was more evident during increased disease activity. Hypermetabolism in the face of increased energy intake continued to cause loss of the FFM. Interleukin-6 correlates with increased REE and erythrocyte sedimentation rate. There was no direct association between IL-6 level and low FFM. We conclude that loss of FFM is common in RA, cytokine production in RA is associated with altered energy metabolism, and preservation of FFM is important in maintaining good quality of life in patients with RA.

Key words Fat-free mass · Nutrition · Resting energy expenditure · Rheumatoid arthritis

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Introduction

Rheumatoid cachexia was first described by Sir James Paget over a century ago.[1] However, this "bad condition" (literal translation from Greek) has not been recognized as a common problem and was underestimated for many decades as cachexia might not be evident on clinical examination alone and patients do not necessarily complain of anorexia; however, since at least a decade ago more medical practitioners who care for rheumatoid arthritis (RA) patients have become increasingly aware of this condition among patients with RA. Patients with RA demonstrate changes in body composition characteristically manifested by progressive erosion of fat-free mass (FFM).[2] Careful assessment of body composition can demonstrate evidence of this wasting syndrome in obese as well as normal and undernourished patients. While cachexia generally connotes a state of advanced malnutrition and wasting, we now know that this term refers to FFM.[3] Furthermore, the reason why loss of FFM is so important is that, in all situations in which it has been studied, starvation, critical illness, and normal aging, loss of greater than 40% of baseline FFM is associated with death.[4–6] Even with as little as 5% loss of FFM

there are demonstrable changes in morbidity, including loss of muscle strength, altered energy metabolism, and increased susceptibility to infections.[7] To put these numbers in perspective, the average loss of FFM among patients with RA is between 13% and 15%,[8,9] approximately one third of the maximum survivable loss of FFM.

It is well recognized that disease processes can interfere with adequate nutrition and even lead to a malnourished state and abnormal body composition. While much attention has been given to surgical conditions, gastrointestinal disease, and cancer, with regard to body composition and energy expenditure, there are few data on patients with inflammatory joint disease, in particular in patients with RA; furthermore, there has been no comprehensive study concerning body composition and energy expenditure in relation to disease activity in patients with RA. It was also noted that high levels of cytokines are found in synovial fluid and in circulation of patients with active RA,[10,11] suggesting that cytokine production might play a contributing role in causing rheumatoid cachexia syndrome. Therefore, the main purposes of our study are: (a) to establish whether in RA patients changes in the body composition mirror changes in disease activity, (b) to investigate the relation between energy expenditure and weight loss, (c) to examine the dietary energy intake and its role in weight loss in RA patients, and (d) to investigate the relation between cytokine (IL-6) and other variables including resting energy expenditure (REE), body composition, and acute phase reactants.

Materials and methods

Study design

A cross-sectional study was conducted on 14 subjects with RA and 14 matched controls comprising patients with noninflammatory diseases such as osteoarthritis (OA) (8 patients), soft tissue rheumatism (4 patients: 2 tennis elbow, 1 de Quervain's tenosynovitis, 2 golfer's elbow), and fibromyalgia syndrome (FMS) (2 patients).

Study population

The study was approved by the local hospital's ethics committee. Subjects with RA were recruited from the rheumatology outpatient clinic. All subjects met the American College of Rheumatology (ACR) 1987 revised criteria for RA.[12] Cases were matched to controls on the basis of age (within 5 years), sex, race, and weight (within 5 kg). Rheumatoid arthritis disease severity was assigned based on the DAS28[13] criteria: DAS28 >3.2 is considered as active while if DAS28 is 3.2 or less, the patients will be considered less active; DAS28 of 2.6 or less will be considered as remission.

Criteria for study inclusion were as follows:

1. Age 18–74 years
2. RA, as defined by the 1987 revised criteria of the ACR

Exclusion criteria were as follows:

1. Concurrent or chronic infection
2. Other inflammatory condition, such as inflammatory bowel disease, connective tissue disease
3. Other diseases that is associated with weight loss (malignancy, diabetes mellitus congestive cardiac failure, etc.)
4. Pregnancy and lactation
5. Those taking medications which affect the metabolic rate, for example, thyroxine, beta blockers, stimulants, etc.

Measurements

The following measurements were made, in order to document: (a) disease activity, including measurement of the tender and swollen joint score as well as the acute phase reactants level in the blood; (b) dietary assessment; (c) body composition (by anthropometry); and (d) energy expenditure (by indirect calorimetry).

Energy expenditure

Resting energy expenditure was measured by indirect calorimetry using the Deltatrac metabolic monitor (Helsinki, Finland). At 08:00 h on the day of the measurements and after an overnight fast of 10–12 h, oxygen consumption and carbon dioxide production were measured over 15–20 min with at least 10 consecutive minutes of stable readings that varied less than 5%. The stable readings were averaged and the mean value was used as the REE for that subject.[14] The Deltatrac monitor has been validated to be accurate to within 98%. The gas chamber of the Deltatrac was calibrated before each measurement using an oxygen bottle containing a mixture of 5% O_2 and 95% CO_2, and the gas volume released at mark 6 on the meter sealing off the bottle top. The measurements were made after the subjects rested supine for half an hour. The subjects were instructed to relax and avoid hyperventilation, fidgeting, or sleep during measurements.

During measurements the head of the patient is covered with a transparent plastic canopy. The Deltatrac monitor generates a constant flow of about 40 l/min through the canopy. In the ventilated hood system, a clear plastic hood is placed over the subject's head and made airtight around the neck with a drawstring. Air is drawn through the system by an adjustable speed fan which maintains a slight negative pressure in the hood. This prevents the escape of expired air from leaks around the neck. The flow through the hood is presented at a rate that is about five to six times greater than the subject's resting minute ventilation. This will produce a steady-state concentration of CO_2 in the hood that is sufficient to achieve accurate measurements but low enough to avoid stimulation of ventilation. All inspired air is then collected into this constant flow and O_2 consumption, CO_2 production, respiratory quotient (RQ), as well as REE are measured simultaneously (Weir equation).[14] The data are displayed on a high-resolution screen. A serial com-

puter interface allows the transfer of measurement results to a data management system.

Clinical assessment of disease activity

1. Joints count for tenderness on pressure and/or pain on motion using the 28 joint count systems[15]
2. Joint count for swelling
3. The modified Stanford health assessment questionnaire (HAQ) was completed by all patients. The HAQ served as an index of disability[16]

Anthropometric measurement (method of assessing FFM)

The height (H) was measured to the nearest 5 mm by using a wall-mounted stadiometer (Holtain Crosswell, Crymych, Dyfed, Wales, UK), with the subject standing erect with no shoes. Weight (W) was measured to the nearest 0.025 kg using a beam balanced scale with the subject in minimal clothing. The scale was calibrated on a regular basis during the study. Skin fold thickness was measured at biceps, triceps, subscapular, and suprailiac sites with Holtan calipers. Arm circumference was measured to the nearest 0.5 cm with a flexible, 1-cm wide tape at mid arm,[17] at the same point where triceps skin fold measurement was done, in the nondominant arm.

All the results were recorded on a special form created to register all anthropometric measurements and to keep in the patient file. The sum of 4 skin folds (S4SKF) was used to derive percentage of body fat or fat mass (FM) by applying the Durnin and Womersly skin fold equation, and FFM was then calculated from the difference between FM in kilograms and body weight.

Dietary assessment

Usual dietary intake was measured by 7 days of nonconsecutive self-administered 24-h diet histories. Each patient was provided with a booklet, the first two pages of which are a demonstration and the rest are the diary records. The method of recording food items emphasizing the importance of accurate measurement and detailed report of the different portions consumed was explained to each patient. The booklet was completed and returned during the measurements day.

Laboratory samples

Blood was obtained from an antecubital vein using a 21-gauge needle and 20-ml plastic syringe. The blood was then divided into special bottles for further testing: 5 ml of hepranized blood to measure Interleukin 6 (IL-6) levels in plasma; 7 ml in an EDTA bottle for erythrocyte sedimentation rate (ESR) levels.

Data analysis

All reported values are means ± SD unless otherwise noted. Comparisons between groups (cases and controls) were analyzed using the Student *t*-test or Mann–Whitney test depending on their distribution. Comparison of REE between groups before and after, adjusted for FFM, was carried out using analysis of covariance. Within-group analysis of the effect of cytokines and other variables on body composition, energy expenditure, and energy intake were carried out using multiple regression techniques to create population-specific modules that were as simple as possible. A P value of less than 0.05 was chosen as indicative of statistical significance.

Results

Demographic and patient characteristics

In total, 28 subjects were studied, 14 RA patients and 14 controls. The control group comprised 8 patients with OA, 4 with soft tissue rheumatism, and 2 FMS patients. Matching was successful for age and sex. Mean RA patient age was 42 (±16) and that of controls 44 (±12). Disease duration was 9.3 years (±7.9) for RA patients and 8.2 years (±5.2) in controls. The difference was not statistically significant for age and duration of disease (Table 1). A significantly higher number of patients with RA who had swollen and tender joints together with higher inflammatory marker (ESR) and functional disease activity index (HAQ) compared to con-

Table 1. Characteristics of patients with rheumatoid arthritis (RA) and matched controls

Characteristics	Patients	Control	*P* value
No. of subjects	14	14	NS
Sex (F/M)	10F/14M	8F/6M	NS
Age (years)	42 ± 16	44 ± 12 NS	NS
Disease duration (years)	9.3 ± 7.9	8.2 ± 5.2 NS	NS
No. of swollen joints	12.1 ± 6.3	0.2 ± 0.12	<0.008
No. of painful joints	14.2 ± 4.1	0.1 ± 0.14	<0.007
ESR (mm/h)	56 ± 12.1	16 ± 5.2	<0.0001
No. of patients taking prednisolone	8	0	
mHAQ	1.95 ± 0.7	0.90 ± 0.9	<0.006

ESR, erythrocyte sedimentation rate; mHAQ, modified Health Assessment Questionnaire; NS, not significant

Table 2. Outcome variables in subjects with RA and controls

	RA patients	Control	*P* value
BMI (w/h^2)	22.1 ± 3.2	25.5 ± 3.5	<0.022
FM (kg)	25.1 ± 9.7	27.2 ± 11.1	NS
FFM (kg)	24.7 ± 9.2	35 ± 12.1	<0.013
FFM/H^2	9.9 ± 3.1	12.9 ± 4.1	<0.027
REE (kcal/day) (unadjusted)	1409 ± 291	1413 ± 288	NS
REE (kcal/day) (adjusted for FFM)	1498 ± 162	1330 ± 206	<0.031
Energy intake (kcal/day)	1820 ± 690	1760 ± 620	NS
IL-6 (U/ml)	132 ± 15	–	–

BMI, body mass index; FM, fat mass; FFM, fat-free mass; H, height; REE, resting energy expenditure; IL, interleukin

Table 3. Linear regression model for outcomes of REE with body composition and clinical variable

Variables	Estimate	SE	*P* value
FFM (kg)	–0.072	0.006	<0.003
IL-6 (U/ml)	26.12	11.22	<0.005
Age (years)	38.16	2.75	NS
Disease duration (years)	7.5	3.45	NS
ESR	36.22	12.56	<0.001
No. of swollen joints	30.48	13.66	<0.005
No. of tender joints	27.67	9.68	<0.004
HAQ score	29.26	14.33	<0.007

Table 4. Linear regression model with FFM as the outcome

Variables	Estimate	SE	*P* value
Intercept	95.27	20.02	<0.05
Energy intake	22.70	15.92	NS
No. of swollen joints	–1.92	0.825	<0.0012
HAQ score	–0.092	0.004	<0.0023
Duration of RA (years)	0.052	0.027	NS
No. of tender joints	–0.063	0.043	<0.0014
ESR (mm/h)	–0.0025	0.0015	<0.0015
IL-6 (U/ml)	19.2	7.6	NS

ESR, erythrocyte sedimentation rate

trols was also noted. Twelve out of 14 RA patients were taking nonsteroidal anti-inflammatory drugs (NSAIDs); 8 were taking prednisolone at the time of the study, with a mean dose of 5.2 mg/day (±3), 3 were on methotrexate (MTX) monotherapy, and 3 on sulfasalazine (SSZ) monotherapy. Eight RA patients were on a disease-modifying agents (DMARDs) combination. Out of 14 RA patients, 5 patients were considered to be in the active disease group and 9 in the lower (or remission) disease activity group. Four patients in the active disease group received either intramuscular or intra-articular steroid within 2 weeks prior to the day of the study.

Body mass index (BMI), FFM, and adjusted FFM were significantly lower in RA patients compared to control despite higher energy intake being noted. When expressed on a whole-body basis, REE did not differ between RA patients and controls. However, when REE was expressed per unit of FFM (adjusted), it was significantly higher in RA patients then in controls. No significant difference of energy intake in RA patients and controls was noted, even though a higher energy intake was noted in patients with RA (Table 2).

Multivariable analysis

To demonstrate and analyze a correlation of REE and FFM with arthopometric/clinical variables, two linear regression models were created. The first model (Table 3) taking REE as the outcome showed a significantly negative correlation with FFM and positive correlation with IL-6, number of tender and swollen joints, ESR, and functional disability index. However, no significant correlation between age and disease duration was noted.

Another linear regression model (Table 4) taking FFM as the outcome showed a significantly negative correlation with number of swollen and tender joints, ESR, and functional disease activity index. However, no significant correlation between energy intake and disease duration was noted.

Further study in subgroups of RA (Table 5) patients comparing clinical and anthropometric variables showed that REE and IL-6 were significantly higher in RA patients with active disease. However, adjusted FFM was higher in a lower/remission group but the difference was not statistically significant. Higher energy intake was noted in patients with active disease but again the difference was not significant.

Discussion

This study clearly shows that hypermetabolism and erosion of the FFM accelerate during times of heightened disease activity and are partially or completely restored during periods of reduced disease activity. We confirmed that hypermetabolism in the face of increased intake continue to cause erosion of the FFM. Loss of body FFM, if unchecked, is fatal. Autopsy studies and data obtained during the starvation of the Jews by the Nazi regime during the Second World War show that loss of >40% FFM is itself lethal in the absence of any other cause of death.[18] Weight loss is a well-documented phenomenon associated with RA.[2] Preservation of FFM is thus important in maintaining good quality of life and resistance to secondary infections.

Weight loss in RA patients differs from that found in simple starvation where more than three-quarters of the

Table 5. Comparison of intake, FFM, REE, and IL-6 in two subgroups of RA

Variables	Active disease ± SD	Low/remission ± SD	*P* value
Mean dietary intake (kcal/day)	32.8 ± 11.6	31.9 ± 10.2	NS
REE (kcal/day)	1520 ± 69	1485 ± 72	<0.032
IL-6 (U/ml)	151 ± 16	110 ± 15	<0.0211
FFM/H^2 (adjusted)	8.1 ± 2.3	9.9 ± 3.9	NS

weight loss arises from adipose tissues and only a small amount from skeletal muscle. In RA cachexia and all other cachexia syndromes, weight is lost equally from adipose tissue and muscle such that for a given degree of weight loss, there is more depletion of skeletal muscle in a cachectic patient than in starving normal subjects. The results of our study have shown that weight and FFM are significantly lower than in controls. We used the height normalized indices of the body's fat-free mass to overcome problems in interpreting the clinical significance of values for FFM in individuals of differing height.[19] We again demonstrated significantly lower FFM in patients when compared with controls. We also demonstrated a significantly negative correlation between low FFM and disease activity indices such as number of swollen and tender joints, inflammatory markers, and functional disease activity score recorded by the patient.

In the subgroup of RA patients, the FFM was slightly higher in remission/lower disease activity than in active disease. This means residual erosion of the FFM still persists despite improved disease activity. We concluded that with repeated flare-ups cumulative residual erosion in the FFM will inevitably grow and ultimately manifest as rheumatoid cachexia syndrome. This might explain the high prevalence of cachexia in RA (67%) demonstrated in previous studies.[20] Our findings also consolidate previous reports which demonstrated that RA cachexia correlates positively with disability score.[20] These variables might indirectly reflect a severe disease course with recurrent flare-ups. Our study did not show any significant correlation of disease duration and rheumatoid cachexia as demonstrated in previous studies,[20] and this might be due to the small number of subjects that were recruited to our study. We intend to expand our study nationwide to include more subjects in our forthcoming study.

Studies in patients with human immunodeficiency virus (HIV) infection demonstrated that reduced energy intake, not elevated energy expenditure, is the prime determinant of weight loss in HIV-associated wasting.[21] Weight loss in cancer patients is a much more complex metabolic problem. Although anorexia is invariably present, the measured food intake does not correlate with the degree of malnutrition. At least a component of weight loss in cancer patients is due to increased REE.[22]

The energy intake in our patients was not reduced; in fact, it was increased compared to controls. Similarly in a study by Koutedakis et al.,[23] 12 patients with chronic RA were compared with 12 healthy controls. Dietary energy intake was not different between patients and controls and insufficient dietary intake was not considered to play a dominant role in causing cachexia in our patients. In sedentary patients REE is the major component of 24-h energy expenditure. Exercise-induced energy expenditure contributes a variable amount, but is relatively small in those patients with low activity levels. We did not record physical activity of patients. We expected a markedly lower level of physical activity in our patients. Despite the general lack of physical activity, the REE remained elevated in RA patients as compared to healthy controls.

It is well known that body FFM is a chief determinant of metabolic rate in nondieting subjects.[24] The decrease in energy expenditure that normally occurs during starvation and weight loss in healthy men and women could not be demonstrated in rheumatoid arthritis patients with weight loss. In our study the data showed that the ratio of REE/FFM increased in patients more than controls despite the fact they have lower weight and lower FFM. Increased weight loss in RA patients was most probably due increased REE rather than reduced intake. Our results are also consistent with previous findings of the association between REE and body composition in rheumatoid arthritis.[8]

Corticosteroids at high doses increase catabolism and cause clinically important nitrogen wasting. The average daily dose of prednisolone taken by our patients was 5.2 mg. Previous studies showed at such levels corticosteroids actually exert a mild protective effect on FFM, perhaps by reducing inflammation[25] and improving appetite. Fat-free mass depletion was seen in patients not taking corticosteroids to a similar extent compared with patients who were on a corticosteroid regimen. We could not show that corticosteroid treatment significantly altered the REE or the body composition in our patients. Further, at the given dose, it is unlikely that MTX would affect energy metabolism in RA.[26] NSAIDs similarly have no effect on REE at anti-inflammatory doses used in our patients.[27]

In testing our a priori hypothesis that inflammatory cytokines lead to disorders of metabolism in RA, we focused on IL-6. We found that higher circulating IL-6 levels were associated with increased REE in the RA group, suggesting that high IL-6 level is linked to hypermetabolism. Cytokine-driven increase in REE has been reported previously in both animal and human studies.[8] We found no direct association between IL-6 level and low FFM. Other studies also failed to demonstrate such a direct association in humans.[8] This is probably because the low FFM is a cumulative outcome over many years while IL-6 level represents the absolute value on the day of the study and does not reflect the summation of cytokine status over many years.

Whether weight loss is ultimately inevitable in RA and whether early aggressive nutritional support can prevent the occurrence of weight loss requires further study. The goals of nutritional care are to support nutritional status,

body composition, functional status, and quality of life. If cachexia is caused by factors other than reduced energy intake, then nutritional support alone is unlikely to completely counter this problem. The catabolic response can be modified and recovery can be accelerated by a variety of approaches such as reducing the inflammatory response, anticachectin factors (anticytokines), and growth factors to enhance protein synthesis and tissue repair. These approaches, whether used alone or in combination, will reduce the loss of body protein, which should accelerate recovery, shorten the length of hospitalization, and reduce convalescence. Knowledge of the mechanism of the induction of cachexia should lead to the development of new therapeutic agents. Attacking the catabolic process of cachexia should lead not only to new anticachectic agents, but also offer the promise of antirheumatic activity, assuming the same mechanism that perpetuates the inflammation in RA induces cachexia.

We conclude that rheumatoid cachexia is a hypermetabolic, hypercatabolic, host-consuming state in which normal starvation-induced adaptive conservation of the body's fuel reserves no longer functions. It is also an important metabolic consequence of RA that can lead to disability and loss of independence, and should be viewed as an important contributor to increased morbidity and premature mortality in RA. Therefore, preservation of FFM is important in maintaining good quality of life in patients with RA. We also conclude that chronic inflammation such as RA can lead to hypermetabolism, and loss of FFM is common in RA. Cytokine production in RA is associated with altered energy metabolism; however, further study of the interactions between production of inflammatory cytokines, FFM, and physiologic function is needed for us to increase our understanding of these changes in health and disease.

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