Low physical activity reduces total energy expenditure in women with rheumatoid arthritis: implications for dietary intake recommendations1–5

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ABSTRACT

Background: Rheumatoid arthritis (RA) causes cachexia, a metabolic response characterized by loss of muscle mass and elevated resting energy expenditure (REE). However, energy expenditure in physical activity in subjects with RA is lower than that in healthy subjects. It is not known which effect predominates in regulating total energy expenditure (TEE), and thus whether the dietary energy requirements of subjects with RA are higher or lower than those of healthy subjects.

Objective: Our objective was to determine TEE in women with RA by using the reference method of doubly labeled water (2H218O).

Design: In this case-control study, we examined 20 women with RA and 20 healthy women who were matched for age and body mass index.

Results: The patients with RA were cachectic (their body cell mass was 14% lower than that of the controls, \( P < 0.001 \)), but REE was not elevated, reflecting good disease control. Mean (±SD) TEE was 1344 kJ/d lower in the patients than in the controls (9133 ± 1335 compared with 10 477 ± 1992 kJ/d; \( P < 0.02 \)). The energy expenditure in physical activity of the patients was 1034 kJ/d lower than that of the controls (\( P < 0.04 \)), which accounted for 77% of the difference in TEE between the 2 groups. The physical activity level (TEE/REE) of the patients also tended to be lower than that of the controls (1.70 ± 0.24 compared with 1.89 ± 0.36; \( P = 0.07 \)).

Conclusion: A low physical activity level is the main determinant of lower-than-normal TEE, and thus energy requirements, in women with RA.

KEY WORDS Rheumatoid arthritis, energy metabolism, doubly labeled water, physical activity, total energy expenditure, women

INTRODUCTION

Rheumatoid arthritis (RA) is the most common type of inflammatory arthritis in adults, affecting ≈1% of the population of developed countries (1), and is an important cause of disability and premature mortality (2, 3). We previously showed that RA is accompanied by a triad of lower-than-normal body cell mass (BCM), elevated resting energy expenditure (REE), and elevated whole-body protein catabolism, which we characterized as rheumatoid cachexia (4–6). Although not intrinsically fatal, rheumatoid cachexia leads to skeletal muscle wasting and can thus reduce muscle strength and quality of life in patients with RA (7–9). In addition, the loss of cell mass is accompanied by a trend toward higher fat mass, with its attendant detrimental effects on health (4, 10).

In previous studies, we found that the degree of disordered metabolism in adults with RA correlated with the amount of tumor necrosis factor-\( \alpha \) and interleukin 1 \( \beta \) produced by peripheral blood mononuclear cells (4). We also found that RA patients who achieved better control of the inflammatory process had energy and protein metabolism that was more similar to that of healthy subjects than was that of RA patients who achieved less control (4, 6). Despite this, aggressive treatment of the inflammation and joint symptoms of RA with the use of disease-modifying agents such as methotrexate does little to reverse rheumatoid cachexia, although it may stop further deterioration (9). Patients with RA continue to have less BCM than do healthy adults and a trend toward higher than normal fat mass.

In a simple form, energy balance can be described by the following equation:

\[
TEE = \text{REE} + \text{TEF} + \text{EEPA}
\]

where TEE is total energy expenditure, TEF is the thermic effect of food, and EEPA is the energy expenditure in physical activity. If weight is stable, energy intake must equal energy output, and TEE must equal dietary energy requirements. Although REE is often elevated in RA, it is not known what effect this has on daily...
TTE and thus dietary energy requirements in patients with RA. In clinical practice, however, where dietary recommendations are usually made on the basis of a multiple of REE, the elevated REE of patients with RA leads to higher recommended dietary intake. However, it is not known whether EEPA, which appears to be lower than normal in RA patients (4), has an appreciable effect on the daily TEE of RA patients, making recommendations based on the elevated REE erroneous. We therefore examined TEE, REE, and EEPA in 20 weight-stable women with well-controlled RA and in 20 healthy control subjects who were matched to the patients for body mass index (BMI; in kg/m²) and age.

SUBJECTS AND METHODS

Subject recruitment

Patients were recruited from the Itzhak Perlman Family Arthritis Center at the New England Medical Center. All patients met the American College of Rheumatology criteria for the diagnosis of RA (11), had been following a stable drug regimen, and were free of disease flare-ups for ≥3 mo before entry into the study. The exclusion criteria were requiring an assistive device to walk; having a clearly disordered gait (limp); participating in regular (>1 time/wk) aerobic or resistance exercise training; having chronic diarrhea, proteinuria, a serum creatinine concentration >1.3 mg/dL, or liver transaminases >2 times the upper limit of the normal range; and using medications known to affect metabolic rate or body composition (β blockers, inhibitors of angiotensin-converting enzyme, estrogen or progesterone, diuretics, and various nonprescription medications). Only women were studied because most patients with RA are women and because of the great expense of doubly labeled water (DLW) and the inability to combine the 2 sexes for statistical analysis permitted only one sex to be studied. Healthy control women were recruited by advertisement and were matched with the patients for age, race, and BMI. All of the controls underwent a screening history, physical examination, and laboratory testing to ascertain that they were healthy. The same exclusion criteria that were applied to the patients were also applied to the controls.

Study protocol

The patients and the controls were admitted to the Metabolic Research Unit at the Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging (HNRCA) at Tufts University for 2 d. On day 1 of the study, REE and body composition were assessed as described below, and questionnaires regarding habitual physical activity and disease activity and severity were administered. The following morning (day 2 of the study), REE was measured a second time, and then a DLW dose was given orally. Five hours after drinking the DLW dose, the subjects were discharged with instructions to 1) collect a daily morning urine sample for 14 consecutive days, 2) immediately freeze and store the urine samples, and 3) return the urine samples to the HNRCA at weekly intervals. In addition, each subject was given a physical activity monitor (see below) to wear on her belt at home during waking hours for the entire 14 d and a 4-d food record to complete on 4 randomly allocated days during the 14-d measurement period. The protocol was approved by the Human Investigations Review Committee of Tufts University and New England Medical Center, and all volunteers gave written, informed consent.

Energy expenditure methods

The goal of the study was to measure TEE and REE and to estimate EEPA, the 3 major components of the energy balance equation. TEE was measured with the use of doubly labeled water, REE was measured with the use of indirect calorimetry, TEF was estimated as 10% of TEE (12, 13), and EEPA was calculated by subtraction of REE and TEF from TEE. Premenopausal women were measured in the luteal phase of their cycle to minimize variability in energy expenditure (14).

The subjects were admitted to the Metabolic Research Unit for an overnight stay. REE was measured with the use of indirect calorimetry for 30 min under thermoneutral conditions in the fasting state (DeltaTrac; SensorMedics Corp, Anaheim, CA). The oxygen and carbon dioxide sensors were calibrated daily with the use of mixed reference gases of known composition, and alcohol burns were performed monthly to prevent instrument drift. The subjects rested in bed in a supine position for 30 min and then had a clear plastic canopy placed over their heads. Room air was pumped through the canopy at a fixed rate (45 L/min). Subjects were instructed to avoid hyperventilation, fidgeting, or falling asleep during the test. REE was calculated with the use of Weir’s equation (15).

On day 2, after the subjects had fasted overnight and voided for the first time in the morning (first baseline urine), REE was measured a second time with the use of indirect calorimetry. After indirect calorimetry, a second baseline urine specimen was obtained, and the subjects drank DLW (0.25 g H₂¹⁸O + 0.15 g H₂O/L total body water). The DLW was given at a set time early in the morning, and the subjects then rested and fasted for 5 h after the dose while hourly urine specimens were collected. In the event that no urine specimen could be collected at one of the time points, 50 mL tap water was given by mouth so that the next collection could be obtained. These specimens were used to measure the dilution spaces of H₂O and H₂¹⁸O in the subjects. They also provided a baseline measure of the abundance of each isotope.

After the dosing regimen, the subjects were instructed on how to collect urine at home and were given collection materials before discharge (16, 17). The final sample was collected when the subjects returned to the HNRCA on the morning of day 14 for final weights. Compliance with the urine collection procedures and the food records was monitored by telephone and with the use of portion-size models for food records as previously reported (9).

Body composition

BCM was measured with the use of a whole body counter and the reference method of whole body counting for total body potassium. The CV for total body potassium measurement at our institution is <5% (18). Dual-energy X-ray absorptiometry was used to measure the whole-body masses of fat, lean tissue, and bone (QDR 2000; Hologic, Waltham, MA). The subjects were scanned in the fasted state in the morning. Whole-body scans were performed in the array mode, and body composition was analyzed with the use of the manufacturer’s software (version 5.64A).

Other measures

A rheumatologist (RR) performed standardized joint examinations and recorded the number of tender and swollen joints, and patients filled out questionnaires about their medications, hours of sleep, smoking status, income, disease duration, and education (10). Self-reported pain and fatigue were queried with the use of 15-cm visual analogue scales (19). Usual EEPA was estimated with the use of a physical activity questionnaire (20). In addition,
Doubly labeled water: analysis and calculations

The abundance of $^3$H and $^{18}$O in dilutions of isotope doses and in urine specimens was analyzed by isotope-ratio mass spectrometry (SIRA-10; Fisons/VG Isogas, Middlewich, Cheshire, United Kingdom) at the HNRCA (22). On average, quadruplicate analyses of each sample were performed, in keeping with current protocols (23). In addition, to independently assess the accuracy of the TEE measurements, blinded samples of known isotopic enrichment were measured on a routine basis.

The DLW data were processed with software written at the HNRCA that uses standard calculation procedures (24). In these calculations, the respiratory quotient values used to convert measured values of the carbon dioxide production rate to TEE were obtained from the 4-d food records, which were analyzed for fat, protein, and carbohydrate content with the use of the USDA Nutrient Database (GRAND, release YVM 879; USDA-ARS, Grand Forks, ND). Errors of underreporting of dietary intake have a smaller effect on respiratory quotients than on estimates of total intake because the respiratory quotient depends on the ratio of fat, protein, and carbohydrate rather than on the absolute amount of fat, protein, and carbohydrate.

Statistical analysis

Data were examined graphically and statistically for normality. The components of energy expenditure were compared between the patients and the controls with the use of unpaired t tests. Analysis of covariance was used to compare energy expenditures and energy intake between the groups after adjustment for differences in body cell mass or body weight, where appropriate. Results were considered statistically significant if the two-sided P value was <0.05. All analyses were performed with the use of SYSTAT or SPSS software (SPSS Inc, Chicago), except sample-size calculations, which were performed with PC-SIZE (25).

RESULTS

Subject characteristics

Twenty women with RA and 20 healthy control women participated in this study. The 2 groups were successfully matched for age, race distribution, and BMI (Table 1). The controls reported no difficulties with joint pain, stiffness, or fatigue. All patients with RA were in functional class I or II (mild-to-moderate impairment) according to criteria from the American College of Rheumatology (26). The patients with RA averaged 4.6 painful joints and 4.9 swollen joints on the day they were examined and reported =1 h of morning stiffness. They reported moderate levels of pain and fatigue (=5 cm on a 15-cm visual analogue scale for each measure). The mean sedimentation rate in the patients was significantly higher (P < 0.04) than that in the controls (29.8 compared with 18.1 mm/h). Nine of the 20 women with RA reported taking prednisone (mean dose: 5.1 mg/d), 9 took methotrexate, 6 took hydroxychloroquine, and 15 took nonsteroidal antiinflammatory medications. Miscellaneous antirheumatic medications included gold (1 patient), minocycline (1 patient), sulfasalazine (1 patient), and azathioprine (2 patients). Overall, these results are compatible with mild-to-moderate RA, suggesting good, but not complete, medical control of the disease.

Nutritional status of patients and controls

As we previously reported, the patients with RA had significantly lower mean (±SD) BCM and bone mass values than did the controls [81.7 ± 10.1 compared with 94.9 ± 11.6 g (P < 0.001) and 2.0 ± 0.4 compared with 2.3 ± 0.4 kg (P < 0.03), respectively] (Table 2). Although the point estimate of mean body fat was higher in the patients than in the controls (27.8 ± 11.1 compared with 25.6 ± 9.9 kg), the difference was not significant (P = 0.52). Six women in each group were overweight (BMI between 25 and 30), and 3 women in each group had a BMI > 30. Mean reported energy intake did not differ significantly between the patients and the controls (6485 ± 1418 compared with 6807 ± 1410 kJ/d, P = 0.47). Protein intake was slightly lower in the patients than in the controls on an absolute basis (47.5 ± 9.9 compared with 55.7 ± 14.4 g/d, P < 0.05) but did not differ significantly when expressed per kilogram of body weight (0.7 ± 0.1 compared with 0.8 ± 0.2 g/kg, P < 0.16). The patients were more likely to smoke than were the controls (25% compared with 5%, P < 0.09) and tended to sleep slightly longer on weekends. Both the patients and the controls underreported dietary energy intake compared with TEE (by 29% and 35%, respectively). All of the subjects maintained their weight during the 14-d DLW measurement period.
Energy expenditure in patients and controls

Mean TEE was 1344 kJ/d lower in the patients than in the controls (9133 ± 1335 compared with 10477 ± 1992 kJ/d; P < 0.02; Figure 1). This difference was largely due to a 27% lower mean EEPA in the patients than in the controls (2849 ± 1075 compared with 3883 ± 1732 kJ/d; P < 0.04; Table 2 and Figure 1). On average, the patients expended 1034 kJ/d less than the controls, which accounted for 77% of the difference in TEE between the 2 groups. Physical activity accounted for 31% of TEE in the patients and 37% of TEE in the controls (P < 0.08). No difference was observed in REE (5372 ± 519 compared with 5544 ± 531 kJ, P = 0.3). REE accounted for 59% of TEE in the patients and 53% of TEE in the controls (P < 0.08). The ratio of TEE to REE, or physical activity level, which is the basis for current World Health Organization recommendations for dietary energy intake, was 1.89 ± 0.35 in the controls and 1.70 ± 0.24 in the patients (P < 0.07). We did not find significant differences in energy variables according to medication use (ie, between those who took prednisone or methotrexate and those who did not) or disease activity (median tender-joint score or median pain scale).

Less expensive methods of assessing EEPA, in which either a belt-worn activity monitor or a standardized questionnaire (Paffenbarger) were used, gave lower estimates of physical activity than did the DLW method (Table 2), and both of the less expensive methods showed poor correlations with the reference method. There was no correlation between the DLW method and the questionnaire (r = 0.25, P < 0.2), and there was only a modest correlation between the DLW method and the activity monitor (r = 0.37, P < 0.04). However, both of the less expensive methods correctly identified the RA group as having a lower level of physical activity than that of the control group (Table 2). Because of differences in the variability of the methods, the number of subjects needed to find a significant difference in EEPA was 19 for the DLW method, 16 for the physical activity monitor, and 35 for the questionnaire.

### DISCUSSION

This is the first study to examine the components of energy metabolism in women with RA and in age- and BMI-matched controls. We found that TEE is significantly lower in patients with RA than in controls because of lower EEPA. The magnitude of the difference in EEPA was large: 1034 kJ/d. To put this in perspective, consider that a 100-kJ/d imbalance in energy expenditure relative to energy intake will lead to a gain or loss in weight of ~1.5 kg over 1 y in a person with 33% body fat. Over a decade, such an imbalance would lead to a 15-kg gain in body weight. Thus, the energy imbalance and degree of physical inactivity observed in our patients was large and could lead to important fat accretion over time.

Although the DLW method is the reference method for assessing TEE and thus EEPA, it is very expensive (~$1000 per subject, including analytic costs, at the time this study was performed), and until recently there was a severe shortage of the oxygen-18 isotope needed to perform such measurements. We therefore examined 2 less esoteric methods of assessing EEPA in patients with RA: a belt-worn activity monitor and a standardized questionnaire. Although neither the activity monitor nor the questionnaire correlated strongly with the DLW method in this population, both methods were able to detect the extreme difference in physical activity observed between the patients and the controls. However, the poor correlations suggest that neither method would be an acceptable substitute for DLW in intervention studies aimed at increasing EEPA in patients with RA. We did not find that patients with RA had more difficulty with either the physical activity monitor or the questionnaire than did the controls; thus, there is no clear reason to suspect differential bias with either method.

We previously showed that a loss of BCM, principally from muscle, is a hallmark of RA. We have termed this loss of BCM “rheumatoid cachexia.” In patients with active RA, we have consistently found an elevated REE as part of this cachexia and have shown that this hypermetabolism is associated with increased
production of the inflammatory cytokines interleukin 1β and tumor necrosis factor-α (4). Moreover, we have shown that production of tumor necrosis factor-α is associated with an increased rate of whole-body protein breakdown and that an anabolic stimulus to muscle, such as strength training, is associated with normalization of this accelerated protein catabolism in RA (6, 10).

The results of this study clearly indicate that low EEPA predominates in determining TEE in patients with RA. In addition, the results of this study suggest that clinicians should not recommend increased dietary energy intake to women with RA despite their risk of elevated REE, because physical activity level—the World Health Organization standard for making dietary energy intake recommendations—in the present study was 10% lower in the patients than in the controls (1.70 compared 1.89).

In the 12 y since we first showed that cachexia is common in RA (27), improvements in treatment have made overt hypermetabolism, defined as elevated REE, less common. This is probably the explanation for the lack of significant difference in REE between the patients and the controls in the present study. For example, the mean erythrocyte sedimentation rate in the patients in the present study was 30 mm/h, whereas the mean erythrocyte sedimentation rate in the patients in our earlier work was 66 mm/h (P < 0.05); the number of swollen or painful joints in the patients in the present study was 5, whereas that number in our earlier work was 8–12 (9). Nevertheless, cachexia continues to be an important problem in RA, as indicated in the present study by the significantly lower BCM of the patients than of the healthy controls, despite fairly aggressive disease treatment and matching for age and BMI. It is likely that in the absence of specific rehabilitative measures, such as strength training, BCM does not spontaneously improve in patients with RA (9).

The combination of decreased EEPA and decreased BCM is a potent force in favor of fat accretion, which suggests that in the future, patients with RA are likely to face an increase in fat mass. There is no evidence at this time that control of inflammation or joint pain reverses the sedentary habits that develop in patients with RA, even though pain relief may be expected to increase physical activity. Concern about obesity in RA is thus warranted, even though pain relief may be expected to increase physical activity. Concern about obesity in RA is thus warranted, even though pain relief may be expected to increase physical activity.

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