Tumor Necrosis Factor-α Production Is Associated with Less Body Cell Mass in Women with Rheumatoid Arthritis

JOSEPH WALSMITH, LESLIE ABAD, JOSEPH KEHAYIAS, and RONENN ROUBENOFF

ABSTRACT. ***Objective.*** To examine the relationship between inflammatory cytokine production and body cell mass (BCM) in women with stable, medically well-controlled rheumatoid arthritis (RA).

Methods. Case-control study of 20 women with RA and 20 healthy women matched for age, race, and body mass index (kg/m^2). Tumor necrosis factor-α (TNF-α), interleukin 1ß (IL-1ß), and IL-6 production were measured by specific, non-cross-reacting ELISA of peripheral blood mononuclear cells (PBMC) cultured with and without 100 ng/ml of endotoxin. Total BCM was assessed by the reference method of whole-body counting of naturally occurring radioactive potassium-40.

Results. Patients with RA were cachectic, with 14% less BCM ($p < 0.001$) and higher TNF-α production ($p < 0.05$) than controls. TNF-α production was inversely associated with BCM both without ($r = -0.51$, $p = 0.03$) and with ($r = -0.57$, $p = 0.01$) endotoxin stimulation in patients but not in controls. In multivariate linear regression models, these inverse associations remained significant after adjustment for age and physical activity. No association was found for IL-1ß or IL-6 production in these models.

Conclusion. Women with stable, medically well-controlled RA have lower than normal BCM that is inversely associated with elevated TNF-α production. (J Rheumatol 2004;31:23–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — CACHEXIA — BODY CELL MASS
TUMOR NECROSIS FACTOR-α — WOMEN

An important metabolic consequence of rheumatoid arthritis (RA) is loss of body cell mass (BCM) known as rheumatoid cachexia. The body's skeletal muscle mass makes up the majority of BCM and is the most labile portion of BCM. Consequently, rheumatoid cachexia leads to muscle wasting and exacerbates disability in RA[1-3]. BCM accounts for over 95% of the body's metabolic activity[4], and is an important predictor of outcome in starvation, critical illness, and normal aging[5]. In all clinical situations in which it has been investigated [e.g., starvation, cancer, and acquired immune deficiency syndrome (AIDS)], a loss of greater than 40% of baseline BCM results in death[6-8]. The average loss of BCM in patients with RA is ~13%[3,9]. Thus, rheumatoid cachexia is thought to be an important contributor to increased morbidity and premature mortality in RA.

Currently, there is no established mechanism for rheumatoid cachexia. However, it develops in the presence of normal protein and energy intake, and in the absence of clinically evident malabsorption and liver and renal dysfunction[9]. Consequently, it is considered a model for the study of chronic hypercytokinemic cachexia. We reported that rheumatoid cachexia is accompanied by elevated resting energy expenditure (REE), accelerated whole-body protein catabolism, low habitual physical activity, and excess production of the inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin 1ß (IL-1ß) by peripheral blood mononuclear cells (PBMC)[9-11]. In addition we have shown that the degree of disordered metabolism in RA correlates with the amount of TNF-α and IL-1ß produced by PBMC[9].

TNF-α and IL-1ß are known to be important mediators of cachexia in cancer and AIDS[12-15], and both cytokines cause protein depletion and muscle wasting when infused into humans and experimental animals[16-21]. TNF-α and IL-1ß, and possibly IL-6, are believed to play central roles in

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the development of rheumatoid cachexia. However, we have not been able to demonstrate a direct relationship between these inflammatory cytokines and depletion of BCM in adults with medically well controlled RA. Consequently, we examined inflammatory cytokine production and body composition in 20 women with stable, medically well controlled RA and 20 healthy control women matched to patients for age, race, and body mass index (BMI, kg/m^2).

MATERIALS AND METHODS

Study population. Patients with RA were recruited from the Itzhak Perlman Family Arthritis Center at Tufts–New England Medical Center. All patients met the American College of Rheumatology (ACR) criteria for the diagnosis of RA[22]. For admission to the study, patients had to be considered under good disease control by their treating rheumatologist. All patients were taking a stable drug regimen and were free of disease flares for at least 3 mo prior to entry into the study. Exclusion criteria included: ACR functional class III or IV, requirement of an assistive device to walk; clearly disordered gait; regular (> 1 time/wk) aerobic or resistance exercise; chronic diarrhea, proteinuria, serum creatinine > 1.3 mg/dl, or liver transaminases > 2× the upper limit of normal; use of medications known or believed to affect metabolic rate or body composition (i.e., beta blockers, angiotensin-converting enzyme inhibitors, estrogen or progesterone, diuretics, anticytokine therapy). Only women were studied because they make up the majority of patients with RA, and because normal body composition differs between men and women. Healthy control women were recruited by advertisement and were matched to patients for age, race, and BMI. All controls underwent a screening history, physical examination, and laboratory testing to ascertain that they were healthy. The exclusion criteria for patients were also applied to the controls.

Study protocol. Patients and controls were admitted to the Metabolic Research Unit at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University for 2 days. On Day 1 of the study, body composition was measured. The following morning (Day 2), resting energy expenditure (REE) was measured and PBMC were isolated from a fasting blood draw taken shortly after measuring REE. Prior to discharge, each subject was given a belt-worn activity monitor (Caltrac; Muscle Dynamics Corp., Torrance, CA, USA) to wear at home during waking hours for 14 consecutive days to estimate habitual physical activity. In addition, each subject was given detailed instructions on how to complete a 4-day food record. Subjects were asked to complete the 4-day food record on 4 randomly allocated days during the 14-day physical activity measurement period. Compliance with food records was monitored by telephone and with the use of portion-size models[3]. The protocol was approved by Tufts University and Tufts–New England Medical Center, and all volunteers gave written, informed consent.

Body composition. BCM was assessed by the reference method of whole-body counting of potassium-40. This method measures total body potassium (TBK), the main intracellular cation, by detecting the amount of naturally occurring radioactive potassium-40 present in the body. Potassium-40 exists at a known and constant natural abundance in the body, and the calculated TBK reflects total intracellular mass or BCM. The coefficient of variation (CV) for potassium-40 whole-body counting at the HNRCA at Tufts University is < 5%[23]. Dual energy x-ray absorptiometry (DEXA) was used to measure total body fat, lean, and bone mass (QDR 2000; Hologic, Waltham, MA, USA). Subjects were scanned in the fasted state in the morning. Whole-body scans were performed in the array mode and body composition was analyzed using the manufacturer's software (version 5.64A).

Cytokine production. PBMC from whole blood samples were isolated by Ficoll-Hypaque centrifugation and washed 3× in sterile, pyrogen-free saline. The PBMC were then suspended at 5×10^6/ml in ultrafiltered RPMI (Sigma Chemical Co., St. Louis, MO, USA) to remove cytokine-inducing substances. The ultrafiltered RPMI was supplemented with 50 µg/ml indomethacin, 100 µg/ml streptomycin, and 100 U/ml penicillin (Sigma), and contained 2% autologous heat-inactivated serum. Following ultrafiltration, the PBMC were cultured in 24-well flat-bottom plates. Each well contained 0.5 ml of cells plus 0.5 ml RPMI or 100 ng/ml lipopolysaccharide (LPS) (*Escherichia coli*, Serotype 055:B5; Sigma) to stimulate TNF-α and IL-1ß production by PBMC. 100 ng/ml phytohemagglutinin endotoxin (Sigma) was used to stimulate IL-6 production by PBMC. After 22 h at 37°C in 5% CO_2, the plates were frozen at –80°C. After this initial freezing, the plates were thawed and frozen 3× to lyse the cells. Measurement of TNF-α, IL-1ß, and IL-6 was by specific, non-cross-reacting ELISA (R&D Systems, Minneapolis, MN, USA). Dilutions of the lysates from endotoxin-stimulated cells were made to obtain measurements in the 40–70% portion of the standard curve. Cell lysates from patients and controls were run in the same assay.

Other measures. REE was measured by indirect calorimetry for 30 min in the fasting state (Deltatrac; SensorMedics Corp., Anaheim, CA, USA) and physical activity was estimated with the use of the belt-worn activity monitor (Caltrac); both were determined as reported[24]. 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[25]. Self-reported pain and fatigue were queried using a standard 15-cm visual analog scale (VAS)[26]. Standard techniques were used to measure Westergren erythrocyte sedimentation rate (ESR) and to perform complete blood counts and chemistry panels.

Statistical analysis. All reported values are mean ± SD unless otherwise noted. Comparisons between groups were made using unpaired t tests or nonparametric tests as appropriate for each variable depending on the normality of its distribution. Comparison of REE and energy intake between groups was made with the use of analysis of covariance after adjustment for BCM or body weight. The associations of cytokines and other variables with BCM were analyzed by univariate linear regression. If the assumptions of linear regression were met, before or after log transformation, multivariate linear regression models were created to adjust for potential confounding variables (e.g., age, physical activity, prednisone use, protein intake, percentage body fat, etc.). The simplest model was used for each analysis. Separate analyses were conducted for the RA group and for the control group, where necessary, and categorical variables were created as needed. All analyses were performed with the use of SPSS software (version 9.0), except sample-size calculations, which were performed with PC-Size[27]. Results were considered statistically significant if the 2-sided p value was < 0.05.

RESULTS

Study population. Twenty women with RA and 20 healthy control women participated in this study. The 2 groups were matched for age, race distribution, and BMI (Table 1). Controls reported no difficulties with joint pain, stiffness, or fatigue. All patients with RA were in ACR functional class I or II[28]. Patients with RA averaged 4.9 swollen joints and 4.6 painful joints, and reported ~1 h of morning stiffness on the day they were examined. Patients also reported moderate levels of pain and fatigue (~5 cm on a 15 cm VAS for each measure). The mean ESR was 29.8 mm/h for patients, 18.1 mm/h for controls ($p < 0.04$). Nine of the 20 women with RA were taking prednisone at a mean dose of 5.1 mg/day; 9 were taking methotrexate (MTX), 6 were taking hydroxychloroquine, and 15 were taking nonsteroidal antiinflammatory medications. Other antirheumatic medications included

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Table 1. Demographic and clinical characteristics of the study participants. Data shown are mean ± SD.

Characteristic	Patients, n = 20	Controls, n = 20	p
Age, yrs*	47 ± 14	48 ± 14	0.90
Race, Black:White*	2:18	2:18	0.90
BMI, kg/m^2*††	25.3 ± 4.5	24.2 ± 3.3	0.50
No. of swollen joints†	4.9 ± 5.1	0 ± 0	0.001
No. of painful joints†	4.6 ± 7.2	0 ± 0	0.001
Morning stiffness, h	1.1 ± 1.5	0 ± 0	0.001
Pain scale††, 0–15 cm	5.5 ± 3.2	0 ± 0	0.001
Fatigue scale††, 0–15 cm	5.2 ± 3.2	0 ± 0	0.001
Duration of RA, yrs	7.7 ± 6.5	0 ± 0	0.001
Mean prednisone dose, mg/day**	5.1 ± 1.7	0 ± 0	0.001
Sedimentation rate, mm/h	29.8 ± 20.4	18.1 ± 12.8	0.04

* Matched variables. ** For the 9 subjects taking prednisone. † Clinical evaluation by a rheumatologist. †† Standard, continuous, 15-cm visual analog scale[26].

gold (one patient), minocycline (one), sulfasalazine (one), and azathioprine (2). No subject had clinical evidence of malabsorption, and all had normal thyroid function, blood counts, hepatic transaminases, and serum concentrations of glucose and insulin. As reported[24], we found no difference in REE, energy intake, or income between patients and controls (Table 2). However, estimated habitual physical activity was markedly lower in patients with RA compared with controls; and cigarette use, as well as duration of weekend sleep, tended to be higher in patients compared with controls (Table 2). Mean protein intake was slightly lower among patients, but this difference was not significant after adjustment for body weight (Table 2).

Body composition. Patients with RA had 14% less BCM compared with healthy controls (81.7 ± 10.1 vs 94.9 ± 11.6 g TBK, $p < 0.001$; Table 2). When the 9 patients taking prednisone were excluded from the analysis to eliminate the potential confounding effect of corticosteroid use, patients not taking prednisone had 16% less BCM compared with controls (79.8 ± 10.1 vs 94.9 ± 11.6 g TBK, $p < 0.001$). There was no significant difference in BCM between patients who were taking prednisone and those who were not. No significant differences in BCM were observed according to use of MTX, measures of disease activity, or disease severity (ACR functional class I vs II). Patients with RA had less lean body mass measured by DEXA compared with controls (35.0 ± 3.2 vs 39.0 ± 3.7 kg, $p < 0.001$), and lean body mass by DEXA correlated strongly with BCM ($r = 0.89$, $p = 0.0001$). Patients with RA had less bone mineral mass than controls (2.0 ± 0.4 vs 2.3 ± 0.4 kg, $p < 0.03$), and

Table 2. Nutritional and lifestyle characteristics of the study participants.

Characteristic	Patients	Controls	p
Weight, kg	65.2 ± 12.8	68.1 ± 11.4	0.46
Body cell mass, g TBK	81.7 ± 10.1	94.9 ± 11.6	0.001
Fat mass, kg	27.8 ± 11.1	25.6 ± 9.9	0.52
Bone mass, kg	2.0 ± 0.4	2.3 ± 0.4	0.03
Resting energy expenditure, kcal/day	1287 ± 118	1338 ± 130	0.30
Physical activity, kcal/day,			
Caltrac activity monitor	302 ± 237	545 ± 351	0.02
Energy intake, kcal/day	1550 ± 339	1627 ± 337	0.47
Protein intake			
g/day	47.5 ± 9.9	55.7 ± 14.4	0.04
g/kg/day	0.7 ± 0.1	0.8 ± 0.2	0.12
Household Income, $/yr			
< $20,000	4	3	
$20,000–$40,000	8	8	0.75
> $40,000	8	9	
Cigarette use, % smokers	25	5	0.09
Sleep, h/night			
Weekday	8.1 ± 1.2	7.7 ± 1.1	0.32
Weekend	8.6 ± 1.0	7.9 ± 1.1	0.08

TBK: total body potassium.

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although the point estimate of mean fat mass was higher among patients (27.8 ± 11.1 vs 25.6 ± 9.9 kg, p = 0.52), fat mass did not differ significantly between the 2 groups.

Cytokine production. No difference was observed between patients with RA and controls for constitutive (unstimulated) production of TNF-α or IL-1ß by PBMC (Figure 1). Constitutive production of IL-6 by PBMC was not measured due to limitations on the number of PBMC available. Production of TNF-α by PBMC stimulated with 100 ng/ml endotoxin was higher in patients compared with controls (2722 ± 2337 vs 1398 ± 1411 pg/ml, $p < 0.05$; Figure 1). Production of IL-1ß by PBMC stimulated with 100 ng/ml endotoxin was not significantly different between patients and controls (4906 ± 3249 vs 3400 ± 3401 pg/ml, $p < 0.19$; Figure 1). There was no difference between patients and controls for production of IL-6 by PBMC stimulated with 100 ng/ml endotoxin (Figure 1).

Cytokine production and BCM. The relationship of PBMC production of TNF-α, IL-1ß, and IL-6 to BCM was examined in patients and controls. We found an inverse association between constitutive TNF-α production and BCM in patients (r = –0.51, p = 0.03; Figure 2A) but not in controls (r = –0.002, p = 0.99; Figure 2A). We also found an inverse association between endotoxin-stimulated TNF-α production and BCM in patients (r = –0.57, p = 0.01; Figure 2B) but not in controls (r = –0.27, p = 0.33; Figure 2B). Constitutive IL-1ß production tended to be inversely associated with BCM in patients (r = –0.43, p = 0.08), but not in controls. No association was observed for endotoxin-stimulated IL-1ß production (r = –0.15, p = 0.58) or endotoxin-stimulated IL-6 production (r = –0.19, p = 0.47) in patients.

In multivariate linear regression models, constitutive TNF-α production was inversely associated with BCM in patients (ß = –5.54, $p < 0.05$; Table 3) but not in controls, after adjustment for age. Endotoxin-stimulated TNF-α production was inversely associated with BCM in patients (ß = –0.002, $p < 0.008$; Table 3) but not in controls, after adjustment for age and physical activity. The sign of the regression coefficient for physical activity was positive for patients in this model (ß = 0.02, $p < 0.05$; Table 3), indicating that the higher the physical activity, the higher the BCM in RA. Prednisone dose, dietary protein and energy intake, smoking status, duration of RA, MTX use, hydroxychloroquine use, nonsteroidal antiinflammatory use, and percentage body fat were not significant explanatory variables in these models. No association was found for IL-1ß or IL-6 and BCM.

Finally, since patients with RA were matched to healthy

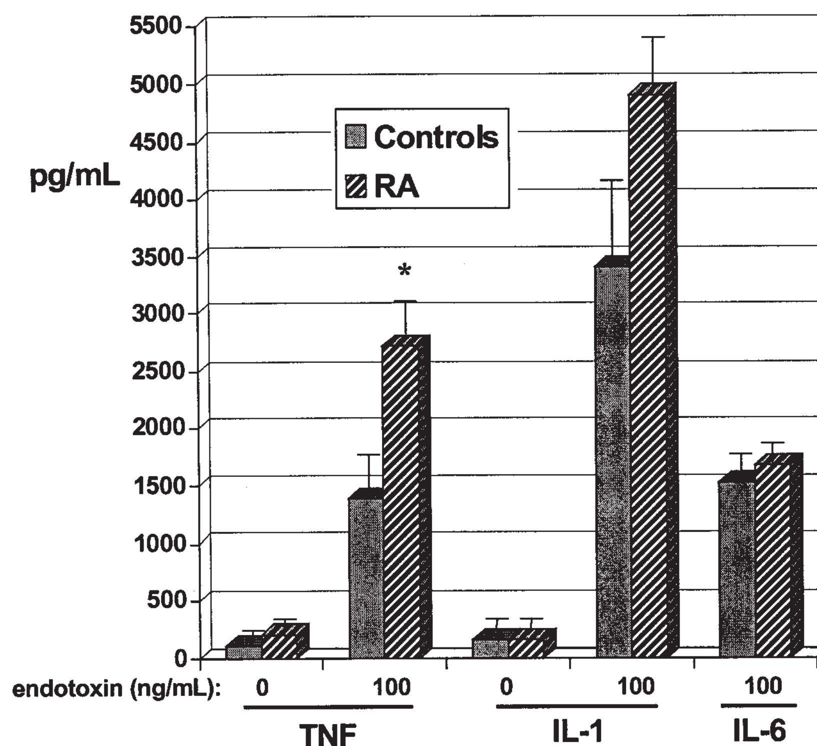

Figure 1. Mean (± SEM) *in vitro* PBMC production of TNF-α, IL-1ß, and IL-6 by healthy controls and patients with RA: with 0 or 100 ng/ml lipopolysaccharide (LPS) stimulation for TNF-α and IL-1ß, and 100 ng/ml phytohemagglutinin stimulation for IL-6. A significant difference was observed between controls and patients for LPS (100 ng/ml) stimulated production of TNF-α. *p < 0.05.

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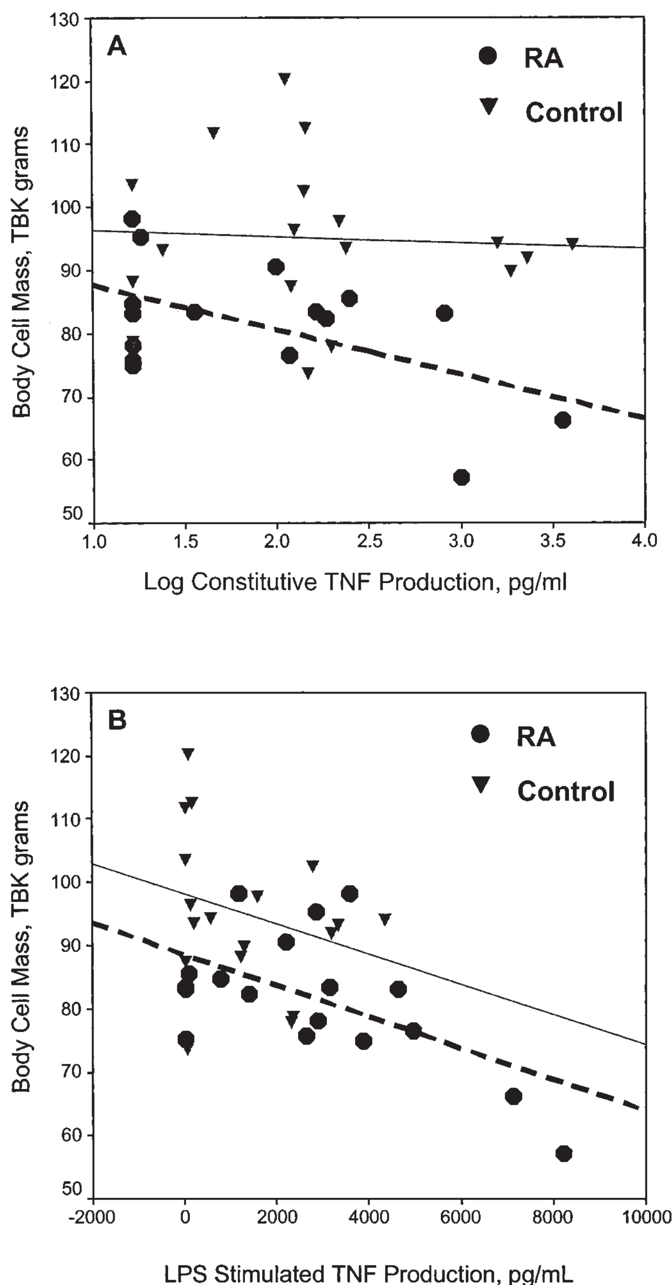

Figure 2. A. Body cell mass (BCM) based on grams of total body potassium (TBK) vs the log of constitutive (unstimulated) TNF-α production by PBMC for healthy controls and patients with RA. A significant inverse relationship was observed for RA patients (r = –0.51, p = 0.03). No relationship was observed for controls (r = –0.002, p = 0.99). In a multivariate linear regression model, constitutive TNF-α production remained inversely associated with BCM in patients with RA (ß = –5.54, p < 0.05; Table 3) after adjustment for age. B. BCM based on grams of total body potassium (TBK) vs LPS (100 ng/ml) stimulated TNF-α production by PBMC for controls and RA patients. A significant inverse relationship was observed for patients (r = –0.57, p = 0.01). No relationship was observed for controls (r = –0.27, p = 0.33). In a multivariate linear regression model, LPS-stimulated TNF-α production remained inversely associated with BCM in RA patients (ß = –0.002, p < 0.008; Table 3) after adjustment for age and physical activity.

controls by BMI, the differences between BMI-matched pairs for BCM and LPS-stimulated TNF-α production were plotted and analyzed. An inverse relationship between the difference in BCM and the difference in LPS-stimulated TNF-α production was observed when healthy control values were subtracted from BMI-matched RA values (r = –0.58, p = 0.03; Figure 3). No associations were found for the difference in BCM and IL-1ß or IL-6 production among the BMI-matched pairs.

DISCUSSION

Data from starvation, critical illness, cancer, and AIDS suggest that a loss of 40% or more of baseline BCM is fatal[6–8,15,23,29]. The results of this study indicate that BCM is 14% lower in women with mild to moderate, medically well-controlled RA compared with healthy women. This difference in BCM is consistent with previous data from our laboratory[3,9], and although a 14% decrement in BCM is not intrinsically fatal, it leads to reduced muscle strength and compromises the ability of patients to cope effectively with metabolic stress.

Erosion of BCM in RA is generally thought to accelerate during times of heightened disease activity when inflammatory cytokine levels are at their highest[3,30-33]. If the BCM that is lost during these periods is not restored during periods of good disease control, the net result is rheumatoid cachexia. In this study, PBMC from women with medically well-controlled RA produced more TNF-α after stimulation by endotoxin than PBMC from healthy women, suggesting that PBMC from women with well-controlled RA are primed to produce higher than normal levels of TNF-α. We propose that over time this contributes to depletion of BCM even in patients with well-controlled RA, particularly if they have experienced periods of increased disease activity prior to medical control of the disease. Given the evidence that TNF-α impairs protein synthesis[34-37] and promotes protein catabolism[12,18,38], it is likely that even moderately high TNF-α levels impair the resynthesis of body protein damaged or lost during periods of disease flare, which leads to depletion of BCM in RA.

Using multivariate linear regression models we found that both constitutive and stimulated TNF-α production were inversely associated with BCM in patients with RA, suggesting that TNF-α has a measurable effect on body composition in women with medically well-controlled RA. In a separate analysis, in which RA patients were paired with healthy controls by BMI, we found that patients with high TNF-α production relative to their BMI-matched healthy counterparts had greater depletion of BCM compared with patients who produced less TNF-α relative to their BMI-matched healthy counterparts. This supports the concept that elevated TNF-α production leads to depletion of BCM in RA.

In contrast to TNF-α, we found a weak inverse associa-

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Table 3. Multivariate linear regression models for the outcome of body cell mass based on grams of total body potassium (g TBK).

Outcome Variable Body cell mass, g TBK	Explanatory Variables	ß	SE (ß)	p
Model Summary	Patients with RA			
$R^2 = 0.490$	Age, yrs	–0.36	0.14	0.02
Adjusted $R^2 = 0.420$	Log constitutive TNF-α	–5.54	2.64	0.05
$p < 0.007$				
$R^2 = 0.670$	Age, yrs	–0.24	0.13	0.09
Adjusted $R^2 = 0.600$	Physical activity, kcal/day	0.02	0.007	0.05
$p < 0.002$	Stimulated TNF-α, pg/ml	–0.002	0.001	0.008
Model Summary	Controls			
$R^2 = 0.260$	Age, yrs	–0.51	0.25	0.07
Adjusted $R^2 = 0.130$	Log constitutive TNF-α	–2.04	3.98	0.62
$p = 0.17$				
$R^2 = 0.320$	Age, yrs	–0.35	0.23	0.16
Adjusted $R^2 = 0.094$	Physical activity, kcal/day	0.009	0.01	0.45
$p = 0.301$	Stimulated TNF-α, pg/ml	–0.001	0.002	0.54

SE (ß): standard error of the regression coefficient ß.

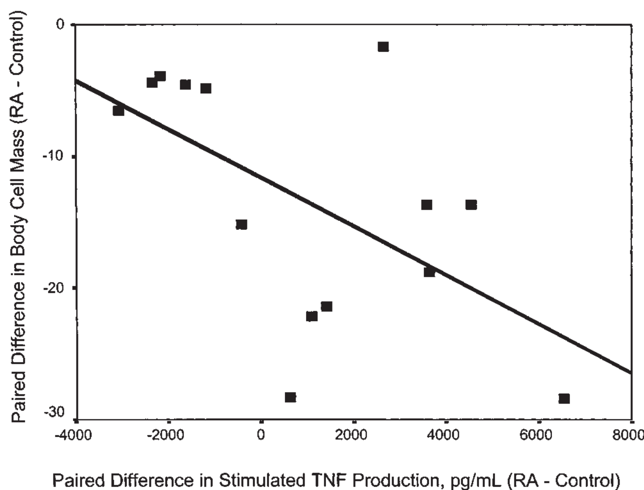

Figure 3. Difference in BCM based on grams of total body potassium vs difference in LPS (100 ng/ml) stimulated TNF-α production by PBMC for BMI-matched pairs (RA – BMI-matched control, squares). A significant inverse relationship was observed (r = –0.58, p = 0.03).

tion between constitutive IL-1ß production and BCM. This contrasts sharply with the equal contribution of IL-1ß and TNF-α to the metabolic disturbances of RA found in our study of patients with more acute disease[9], and suggests a less significant role for IL-1ß in women with medically well-controlled RA. We did not find an association between IL-6 production and BCM, indicating that IL-6 is not an important mediator of cachexia in well-controlled RA. However, IL-1ß and IL-6 are known to cause cachexia[13,20,21,39-41], and both cytokines are elevated in RA during periods of disease flare[31-33]. Thus, IL-1ß and IL-6, in conjunction with TNF-α, may be important mediators of rheumatoid cachexia during periods of heightened disease activity.

This is the first study, to our knowledge, to examine body composition and inflammatory cytokine production in patients with good clinical disease control and uniformly low disease severity. This is important, because our earlier work revealed a strong dose-response relationship between disease severity and depletion of BCM in patients with RA[3,9]. By limiting disease severity, we limited the potential confounding effect of high-dose corticosteroids on BCM. Indeed, we did not observe a difference in BCM between the 9 patients who were taking prednisone (mean dose 5.1 mg/day) and those not taking prednisone. In addition, the patients who were not taking prednisone had 16% less BCM than their healthy counterparts, indicating that low-dose prednisone is not an important determinant of rheumatoid cachexia.

In the 13 years since we first showed that cachexia is common in RA[42], improvements in treatment have made elevated REE less common. This is probably the explanation for the lack of difference in REE observed in this study. More specifically, the mean ESR for the patients in this study was 29.8 versus 70.7 mm/h in our earlier work[3]; and the mean number of swollen and painful joints was 4.8 in this study compared with 7.2 in our earlier work[3]. Nevertheless, these data indicate that cachexia is a consequence of RA even when REE is normalized and good clinical disease control is achieved. This strengthens the need to direct therapeutic interventions at the specific causes of rheumatoid cachexia. These data reinforce the importance of investigating anti-cytokine therapy, and specifically anti-TNF-α therapy, as a means of restoring BCM in patients with RA.

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