Cigarette smoking significantly increases basal metabolic rate in patients with rheumatoid arthritis

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ABSTRACT

Objective: Basal metabolic rate (BMR) is the most important indicator of human metabolism and its abnormalities have been linked to undesirable health outcomes. Cigarette smoking associates with increased BMR in healthy individuals; it is also related with worse disease outcomes in patients with rheumatoid arthritis (RA), in whom BMR is high due to hypercatabolism caused by systemic inflammation. We aimed to investigate whether smokers with RA demonstrated higher BMR levels than their non-smoking counterparts.

Methods: A total of 53 patients with RA (36 female, 17 male, 20 current smokers) were assessed for: BMR (indirect calorimetry), anthropometrical data, fat-free mass (bioelectrical impedance), physical function (health assessment questionnaire; HAQ) and disease activity (disease activity score DAS28 and C reactive protein).

Results: RA smokers and non-smokers were not significantly different for age, height, weight, body mass index and fat-free mass. Compared to non-smokers, smokers with RA demonstrated significantly higher BMR (mean (SD) 1513.9 (263.3) vs 1718.1 (209.2) kcal/day; $p < 0.001$) and worse HAQ (1.0 (0.8) vs 1.7 (0.8); $p = 0.01$). The BMR difference was significantly predicted by the interaction smoking/gender ($p = 0.04$). BMR was incrementally higher in light, moderate and heavy smokers ($p = 0.018$), and correlated with the daily number of cigarettes smoked ($r = 0.68$, $p = 0.04$).

Conclusion: Current cigarette smoking further increases BMR in patients with RA and has a negative impact on patients' self-reported functional status. Education regarding smoking cessation is needed for the RA population.

Basal metabolic rate (BMR), the main indicator of human metabolism, is a vital physiological function providing for bioenergetics, body composition and by-product removal, and is largely affected by perturbations of the body's internal and/or external environment.¹ Inflammatory disease,^{2–3} cancer,⁴ human immunodeficiency virus infection,⁵ critical illness,⁶ as well as active⁷ and passive⁸ smoking are factors that significantly increase BMR and disturb normal metabolic processes.

Rheumatoid arthritis (RA), the commonest chronic inflammatory joint disease, is accompanied by a set of metabolic abnormalities collectively referred to as rheumatoid cachexia. This abnormal metabolic response is mainly due to excessive production of tumour necrosis factor alpha (TNF α): this causes significant elevation in BMR and enhances protein catabolism, resulting in involuntary and rapid wasting of muscle mass.⁹ Rheumatoid cachexia has also been closely asso-

ciated with augmented abdominal fat deposition¹⁰ increased cardiovascular risk,² and compromised muscle strength, balance and functional ability; as such, it is a significant overall contributor to comorbidity and reduced life-expectancy in RA.¹¹ Ideally, any factors associated with increasing metabolism in RA should be identified and, if possible, eliminated early in the course of the disease.

In healthy subjects, current cigarette smoking significantly augments resting metabolism.¹² The impact of smoking on BMR has not been assessed in patients with RA. However, smoking has been implicated in the aetiology,^{13–14} severity¹⁵ and cardiovascular co-morbidity^{16–17} of this disease. The aim of the present study was to investigate whether RA patients who are current cigarette smokers have higher BMR levels than RA patients who have never smoked.

METHODS

Participants

A total of 53 consenting volunteers (36 females, 17 males; 20 current cigarette smokers, 33 non-smokers) with RA were recruited from rheumatology outpatient clinics of the Dudley Group of Hospitals NHS Trust in the UK. All patients met the retrospective application of the revised 1987 American College of Rheumatology (ACR) classification criteria¹⁸ as well as the inclusion and exclusion criteria for this study (table 1). The presence or absence of inclusion/exclusion criteria was on the basis of patient history and was further verified by review of hospital and, where necessary, primary care notes, all their medications and relevant blood tests (eg, thyroid function tests, fasting glucose, liver function tests). The patients included in this study comprised a subgroup of a larger group of 82 RA patients recruited consecutively from these clinics for assessment of BMR, as part of another study. The present study however, included only patients who had never smoked or were current cigarette smokers: ex-smokers, and patients smoking cigars, pipes or other substances were excluded. Smokers were further divided into three subgroups according to the number of cigarettes smoked per day (light smokers: < 5 , moderate smokers: 5–9, heavy smokers: ≥ 10). RA patients had to be on stable medication for at least 3 months prior to assessment.

Information was given to all participants in verbal and written format, and a special follow-up visit was arranged in the rheumatology research unit for final consent and assessment. The study had prior approval by the local research ethics

Table 1 Inclusion and exclusion criteria for the current rheumatoid arthritis (RA) patients

Inclusion criteria	Exclusion criteria
Patients fulfilling 1987 American College of Rheumatology classification criteria for RA, irrespective of age, sex, disease activity, disease duration, treatment or anthropometrical characteristics.	Hyper- or hypothyroidism
On stable medication for ≥ 3 months prior to assessment	Diabetes mellitus
	Malabsorption of any cause
	Chronic liver failure
	Pregnancy
	Current or chronic diarrhoea
	Proteinuria
	Obstructive or restrictive lung disease
	Congestive heart failure
	Current infection
	Ex-cigarette smokers, or current cigar, pipe or other substance smokers

committee and the Dudley Group of Hospitals Research and Development Directorate.

Procedures

All participants attended a single 2 h laboratory session after visiting the data collection site early in the morning (8:00–9:00 a.m.) following a 12-h overnight fast. Demographic and anthropometrical characteristics were recorded first, BMR was measured next, and a blood sample with assessment of the disease activity score (DAS28)¹⁹ and health assessment questionnaire (HAQ) were performed last. Standing height was measured to the nearest 0.5 cm (Seca Stadiometer 208, Vogel & Halke, Hamburg, Germany). Body mass was measured to the nearest 0.1 kg and body composition was evaluated by bioelectrical impedance, using a segmental body composition analyser (Tanita BC 418 MA, Tanita, Tokyo, Japan). Several other methods for assessing body composition, such as dual energy x ray absorptiometry, underwater weighing, total body water, and total body nitrogen may be superior for studies assessing specifically body composition,^{20, 21} but are cumbersome and require specialised equipment and personnel. Bioelectrical impedance, particularly based on eight electrodes as in this study, has been shown to be accurate in the general population²² as well as in patients with RA,²⁰ and has the advantage of simplicity and reproducibility in the routine clinical setting.¹⁰ BMR was measured via indirect calorimetry, adhering to well-described methodological standards.²³ Participants rested for a 20-min period prior to the measurement in a semi-darkened, quiet and thermoregulated (22°C) room. An automated gas analyser (Metalyzer, Cortex Biophysik, Borsdorf, Germany), calibrated before each test using standard gases of known concentration, was used to record respiratory parameters every 20 s, while subjects inspired room air through a free-breathing face mask. Data were collected over a period of 40 min with the participants being instructed to refrain from sleeping or hyperventilating. Mean values of BMR for that period excluding the first and last 5 min were calculated using the Weir equation.²⁴ Contemporary RA disease activity was measured using the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), both routinely measured in the laboratories of the Dudley Group of Hospitals; and clinically using the DAS28¹⁹ performed by a single specialist metrology nurse. Disease

severity (reflected in physical dysfunction) was assessed using the HAQ. Disease duration (from symptom onset) was recorded.

Statistical analyses

Routine pre-analysis screening using the Kolmogorov–Smirnov normality tests were conducted to detect whether the studied variables were normally distributed. Comparisons between RA smokers and non-smokers for the three not normally distributed variables (ie, disease duration, CRP and ESR in table 2) were conducted using non-parametric tests (Mann–Whitney U test), and results are presented as median (range). All other (normally distributed) variables were compared using parametric statistics (Student t tests) and results are presented as mean (SD). For statistically significant differences in normally distributed variables between the smoker and non-smoker RA groups, the 95% confidence intervals (95% CI) are also reported. One-way ANOVA was adopted to examine whether mild, moderate and heavy RA smokers had different levels of BMR. Pearson's and Spearman's correlations were employed, as appropriate, to assess whether parameters previously reported to influence BMR, ie demographic (gender, age), anthropometrical (height, weight, body mass index (BMI) and fat-free mass (FFM)) and disease related (CRP, DAS28, ESR)^{1, 2, 9, 25} showed associations with BMR in these RA patients. ANCOVA was used to detect if smoking was a significant factor influencing BMR after adjusting for variables that were found to significantly influence BMR. All statistical analyses were conducted using SPSS (version 13.0.1, Chicago, Illinois, USA), and statistical significance was set at $p < 0.05$.

RESULTS

Demographic, anthropometrical and disease-related characteristics, are shown in table 2. There were no significant differences between RA smokers and non-smokers in any of the parameters assessed apart from disease severity as assessed by the HAQ and BMR: HAQ physical disability was significantly worse (mean (SD) 1.66 (0.8) vs 1.04 (0.8); $p = 0.01$, 95%CI –1.1 to –0.1), and BMR was significantly higher (1718.1 (209.2) vs 1513.9 (263.3) kcal/day; $p < 0.001$, 95% CI –343.4 to –65.1) in smokers compared to non-smokers (table 2). Within RA smokers, BMR levels were significantly different between the light (1523.8 (192.3) kcal/day), moderate (1723.4 (180.7)) and heavy (1850.7 (154.6) kcal/day) smokers ($p = 0.018$). The number of cigarettes smoked correlated significantly with BMR ($r = 0.61$, $p = 0.04$). A similar, but non-significant ($p > 0.05$), difference was found for the HAQ between light (1.4 (0.9)) moderate (1.6 (0.9)) and heavy (1.9 (0.8)) smokers.

In the entire cohort of RA patients ($n = 53$), BMR showed significant correlations with age ($r = -0.36$, $p = 0.008$), height ($r = 0.59$, $p < 0.001$), weight ($r = 0.71$, $p < 0.001$), BMI ($r = 0.51$, $p < 0.001$) and FFM ($r = 0.72$, $p < 0.001$). In addition, BMR significantly correlated with CRP and DAS28 ($r = 0.36$, $p = 0.008$ and $r = 0.27$, $p = 0.47$, respectively). ANCOVA showed that after adjustment for the factors that significantly correlated with BMR, the difference in BMR was significantly attributed to the association of smoking/gender ($F_{1,38} = 4.3$, $p < 0.05$) but not either of these factors alone (smoking $F_{1,38} = 0.59$, $p > 0.05$; gender $F_{1,38} = 0.14$, $p > 0.05$); despite the fact that, no significant differences were observed in the factors that influence resting metabolism between female smokers and non-smokers (mean (SD) age: 57.1 (13.6) vs 62.9 (10.9) years; BMI: 25.4 (5.9) vs 25.7 (4.1) kg/m², FFM: 41.6 (6.0) vs 40.5

Table 2 Demographic, anthropometric and disease-related characteristics for the rheumatoid arthritis (RA) patients assessed in this study

	RA Smokers (n = 20)	p	RA non-smokers (n = 33)	Total RA (n = 53)
Demographic				
Gender				
Males	5	–	12	17
Females	15		21	36
Age (years, mean (SD))	58.2 (12.0)	0.07	64.1 (11.2)	61.9 (11.7)
Anthropometrical				
Height (cm, mean (SD))	164.5 (9.8)	0.26	161.6 (8.8)	162.7 (9.2)
Weight (kg, mean (SD))	72.5 (19.7)	0.32	67.7 (15.0)	69.5 (16.9)
Body mass index (kg/m ² , mean (SD))	26.2 (5.8)	0.69	25.7 (4.4)	25.9 (4.9)
Fat free mass (kg, mean (SD))	45.8 (10.8)	0.46	44.6 (9.4)	45.1 (9.8)
Disease-related				
C-reactive protein (mg/L)	14.5 (7.2–35.2)	0.22	10.0 (7.0–18.0)	10.0 (7.0–27.0)
Disease activity score 28 (mean (SD))	4.6 (1.5)	0.14	4.1 (1.1)	4.3 (1.2)
Erythrocyte sedimentation rate (mm/first h)	24.5 (10.5–41.7)	0.58	20 (10.5–31.0)	22.0 (10.5–35)
Disease duration (years)	7.5 (5.2–19)	0.94	10.0 (3.0–16.0)	9.0 (5.0–16.0)
Health assessment questionnaire (mean (SD))	1.7 (0.8)	0.01 95% CI –1.1 to –0.1	1.0 (0.8)	1.3 (0.9)
Basal metabolic rate (kcal/day, mean (SD))	1718.1 (109.2)	<0.001 95% CI –343.4 to –65.1	1513.8 (263.3)	1590.9 (262.0)

Significant differences were only detected between BMR and HAQ between smokers and non-smokers with RA.

(4.0) kg; CRP: 11.0 (6.0–38.0) vs 10.0 (6.0–14.0) mg/L, respectively, all at $p > 0.05$), BMR was significantly increased in the former group (female smokers: 1652.2 (202.4) vs non-smokers: 1452.1 (180.7) kcal/day, respectively, $p = 0.001$ and 95% CI –394.1 to 120.4). A similar trend was observed in males (smokers: 1810.4 (101.6) vs non-smokers: 1690.6 (327.1) kcal/day), however, this was not significant ($p > 0.05$). Smoking appeared to be a more powerful predictor of BMR than either CRP ($F_{1,38} = 1.0$, $p = 0.31$) or DAS28 ($F_{1,38} = 0.03$, $p = 0.86$).

DISCUSSION

This study shows that current cigarette smokers with RA have significantly higher BMR than patients with RA who have never smoked. As previously described in normal^{19,25} and diseased^{26–29} populations, BMR in the total group of RA patients studied here was influenced by several demographic and anthropometrical characteristics (including age and FFM), as well as inflammatory disease activity.^{2,3,9} The groups of RA smokers and non-smokers were not significantly different for any of these characteristics, and the difference in BMR remained robust even after statistical adjustment for them, suggesting that it was predominantly, if not exclusively, due to smoking.

The expected BMR in healthy normal individuals of similar age and anthropometrical characteristics to the patients studied here would be approximately 1400 kcal/day.³⁰ RA non-smokers in this study had a mean BMR 8% higher (just over 1500 kcal/day) while RA smokers demonstrated a mean BMR 20% higher than this (over 1718 kcal/day). A BMR increase of more than 12% above normal levels has been reported to have detrimental health implications, particularly when the extra energy derives from muscle catabolism.^{2,3} Active RA⁹ or smoking³¹ may independently or in tandem result in loss of FFM, leading to compromised muscle strength and balance, functional disability, and immune dysfunction.¹¹ It seems reasonable to suggest therefore, that through such a mechanism, smoking may further enhance the deleterious consequences of ongoing inflammation in RA, and this would be partly supported by the finding in the present study that RA smokers had worse physical function than non-smokers, as assessed by the HAQ.

The suggestion that smoking plays an important role is further supported by the finding that smoking appears to be a stronger predictor of increased BMR than disease activity, and

of a stepwise BMR increase between light, moderate and heavy smokers, together with the direct significant correlation between BMR and the number of cigarettes smoked, and the finding that the smoking/gender interaction is a significant predictor of BMR. These results reveal that it is female patients that have the most pronounced effects in BMR as a result of smoking; the same trend was observed in males but it was not statistically significant, probably due to the small number of male smoking RA patients included in this study. Overall, these findings suggest that smoking causes a dose-dependent increase in BMR, which is in line with previous reports in normal populations.^{7,12} Acute (eg, immediate increase in oxygen demand³²) and chronic (eg, elevated thyroxine levels³³) physiological changes due to smoking may account for increases in BMR.

Smoking in RA has attracted considerable research interest for many years. Smoking is a factor that has been linked to the aetiopathogenesis of the disease,^{34–37} particularly in the context of concurrent genetic predisposition.^{13,14} It appears to associate with greater disease activity and overall severity^{15,38,39} as well as extra-articular manifestations including rheumatoid nodules,⁴⁰ vasculitis¹⁷ and accelerated atherosclerosis.¹⁶ Smoking has also been linked to imbalances in the production of TNF α and soluble TNF receptors, leading to a relative excess of TNF α .⁴¹ This may be one of the mechanisms leading to the increased hypermetabolism specifically in RA smokers, as observed in the present study.

Although this study did not intent to identify the clinical implications of the increased BMR due to smoking, it could be argued that the significant increase in HAQ, suggests that smoking negatively affects the patients' self-reported functional status. Smoking, together with age, gender, education, exercise, BMI and number of co-morbidities, have previously been described as important determinants of HAQ disability.⁴² Hypermetabolism in RA has also been linked to increased disability, reduced quality of life and premature mortality;^{2,11} it is likely that the additional smoking-induced elevation of BMR will have further negative effects (eg, increased protein catabolism) on the health status of this population. The present findings add further reasons to suggest that the RA population has to be specifically targeted for smoking cessation.⁴³

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