Clinical and Experimental Rheumatology 2009; 27: 985-988.

Rheumatoid cachexia and cardiovascular disease

G.S. Metsios[1,2,3], A. Stavropoulos-Kalinoglou[1,2,3], V.F Panoulas[2], A. Sandoo[2], T.E. Toms[2], A.M. Nevill[1], Y. Koutedakis[1,3], G.D. Kitas[2]

[1]School of Sport Performing Arts and Leisure, University of Wolverhampton, Walsall, West Midlands, United Kingdom; [2]Department of Rheumatology, Dudley Group of Hospitals NHS Trust, Russell's Hall Hospital, Dudley, West Midlands, United Kingdom; [3]Research Institute in Physical Performance and Rehabilitation, Centre for Research and Technology – Thessaly, Trikala, Greece.

George S. Metsios, PhD
Antonios Stavropoulos-Kalinoglou, PhD
Vasileios F. Panoulas, PhD
Aamer Sandoo, MSc
Tracey E. Toms, MD
Alan M. Nevill, PhD
Yiannis Koutedakis, PhD
George D. Kitas, MD, PhD

Please address correspondence to:
Dr George S. Metsios,
School of Sport Performing Arts and Leisure, University of Wolverhampton, Wolverhampton, West Midlands, United Kingdom.
E-mail: G.Metsios@wlv.ac.uk

Received on March 23, 2009; accepted on June 19, 2009.

Key words: Rheumatoid arthritis, rheumatoid cachexia, body mass index, obesity, cardiovascular disease, mortality, morbidity, prevalence, medication, fat-free mass, body composition.

Competing interests: none declared.

ABSTRACT

Objective. *It has been frequently stated that rheumatoid cachexia (RC) associates with increased cardiovascular risk; however, no studies to date have investigated this. The aim of this study was to investigate the association of RC with multiple novel and classical cardiovascular disease (CVD) risk factors and the presence of established CVD in rheumatoid arthritis (RA).*

Methods. *A total of 34 RA patients with RC (RA+RC) were identified from a database of 400 RA patients using published RC criteria and compared to the remaining patients (RA-RC) who did not fulfil RC criteria. All patients were assessed for fat and fat-free mass, albumin (indicator of catabolism), disease activity/severity, novel and classical risk CVD factors and established CVD.*

Results. *Fat-free mass (kg) and albumin (g/L) were significantly decreased in RA+RC vs. RA-RC patients: 37.3(33.9–41.6) vs. 45.9(41.2–55.5), p<0.001 and 39.6±6.7 vs. 42.4±4.9, p=0.001). Percent body fat was not significantly different. No significant differences were detected in either the classical or novel CVD risk factors, 10-year CVD risk or the prevalence of established CVD.*

Conclusions. *RC does not appear to be associated with worse CVD profile in RA patients, but this needs to be confirmed in prospective studies.*

Introduction

Rheumatoid arthritis (RA) is characterised by systemic inflammation and associates with increased morbidity and mortality from cardiovascular disease (CVD). It also leads to a metabolic abnormality, rheumatoid cachexia (RC) (1-3), characterised by excessive involuntary wasting of fat-free mass; this is rarely reflected in changes of weight or body mass index (BMI), because it may be masked by increased fat mass (2, 4). RC is attributed mainly to reduced physical activity and increased production of pro-inflammatory cytokines, particularly tumour necrosis factor alpha (TNF-α), which alter normal protein metabolism towards a catabolic state (3). Preliminary evidence suggests that RC may be reversed using exercise and high-protein diet (5, 6). Regarding TNF-α biologics the available data are still inconclusive; however, it has been found that TNF-α inhibition increases physical activity mainly due to improved physical function (7) as well as protein intake, possibly due to an increase in ghrelin (8).

It has been suggested that RC associates with increased CVD (9), but there are no studies that have directly investigated this. The aim of the present study was to investigate whether RC associates with worse classical or novel CVD risk factor profile, cumulative 10-year risk for CVD, or prevalence of CVD in patients with RA.

Materials and methods

The Dudley RA comorbidity cohort (DRACCO), a large prospective cohort of 400 RA patients whose clinical, laboratory, metabolic, demographic and anthropometric characteristics have been previously described in detail (10), was utilised in this study.

RC was defined by recently published criteria (11) which are based on well-established, age-related, cut-off points set by bioelectrical impedance: fat-free mass index (FFMI) below the 10th percentile, and fat mass index (FMI) above the 25th percentile (12). All patients with RC (RA+RC, n=34) satisfying these criteria were identified and compared - for classical and novel CVD risk factors, 10-year CVD risk and prevalent CVD - with all remaining 366 patients from the cohort who did not satisfy RC criteria (RA-RC, n=366).

Height was recorded on a Seca Stadiometer (Vogel & Halke & Co., Hamburg, Germany). Weight and segmental body composition were evaluated by bioelectrical impedance (Tanita BC418MA, Tokyo, Japan): fat-free mass and fat-mass data were then used to calculate the fat-free mass index-FFMI (fat-free mass (kg)/height^2) and fat mass index-FMI (fat mass(kg)/height^2) (12). Classical and novel CVD risk factors assessed in fasting blood included: Triglycerides, total cholesterol, high-density lipoprotein, calculated low-density lipoprotein (LDL) (Vitros® 5.1 FS chemistry system, USA); glucose and insulin (Immunolite 2000 Analyser, Diagnostic

Products Corporation, USA); Type I plasminogen activator inhibitor antigen, tissue-type plasminogen activator antigen (Asserchrom, Diagnostica Stago, France), homocysteine (fluorescent polarization immunosorbent, Abbott laboratories, USA), apolipoprotein B, C-reactive protein (CRP), serum uric acid (Vitros® 5.1 FS, USA), interleukins (IL)-1b, IL-6, TNF-α (multi-analyte Biochip Array Technology, Randox, USA), haemoglobin, white cell count (ADVIA® 120 Hematology System, Bayer Healthcare), fibrinogen and von Willebrand Factor (IL Futura Advance analyser, UK). Albumin was also measured, as an indicator of protein loss.

Statistical analyses

After assessing normal distribution, either ANOVA or Mann-Whitney tests were used to assess the differences between the two groups, as appropriate. Values are reported either as mean±SD or median (interquartile range). Comparisons of categorical variables were conducted using Chi-square tests. Multivariable models were conducted to investigate the prediction power of pro-inflammatory cytokines and methotrexate against cachexia. Statistical analyses were conducted using SPSS (version 13.0.1, Chicago, Illinois), with statistical significance set at $p<0.05$.

Results

Population characteristics

Demographic, anthropometric and clinical characteristics, as well as medication use in the group of RA patients with RC (RA+RC) and the remaining RA patients without RC (RA-RC) are shown in Table I. Significant differences were present in most anthropometric and some clinical characteristics. TNF-α and IL-1β levels were significantly increased in the RA+RC group (Table I). Moreover, TNF-α and IL-1β were strong predictors of cachexia (F=3.7, p=0.04 and F=5.4, p=0.022, respectively); this significant prediction persisted even after adjustment for DAS28 and HAQ (TNF-α: F=4.6, p=0.034 and IL1β: F=7.5, p=0.008). Finally, the use of methotrexate was not predicted by cachexia; its strongest predictor in all models was disease severity (HAQ, p=0.008).

Table I. Demographic, anthropometric and clinical characteristics of the study populations.

	RA+RC (n=34)	RA-RC (n=366)	*p*-value
General demographics			
Age (years)	68.3 (64.7–73.0)	62.7 (54.0–69.4)	<0.001
Sex female n (%)	27 (80%)	265 (72.4%)	NS
Smoking status current smokers n (%)	8 (24.2%)	57 (15.9%)	NS
Anthropometric			
Height (cm)	164.0 (159.7–170.0)	162.5 (157.0–170.0)	NS
Weight (kg)	59.2 (51.4–65.5)	74.4 (65.8–85.2)	<0.001
Body mass index (kg/m^2)	21.7 ± 3.5	28.3 ± 4.7	<0.001
Fat-free mass (kg)	37.3 (33.9–41.6)	45.9 (41.2–55.5)	<0.001
Fat mass (%)	35.4 (28.8–37.6)	36.2 (30.4–41.8)	NS
RA characteristics			
General characteristics			
RF positive n (%)	8 (25.0%)	87 (24.2%)	NS
Disease duration (years)	11.0 (6.0–20.5)	10.0 (4.0–18.0)	NS
Disease activity			
C-reactive protein (mg/L)	6.5 (4.0–14.0)	9.0 (5.0–20.0)	0.023
ESR (mm/1hr)	16.5 (9.7–39.0)	21.0 (9.0–37.0)	NS
Disease Activity Score	284.3 ±1.8	4.2 ± 1.4	NS
Interleukin 1b (pg/ml)	5.7 (1.9–39.0)	1.1 (0.0–7.4)	0.020
Interleukin 6 (pg/ml)	11.4 (8.2–19.9)	13.6 (9.6–21.3)	NS
TNF-α (pg/ml)	34.2 (7.2–112.3)	7.5 (5.0–32.8)	0.027
Disease severity			
HAQ	1.6 (0.3–2.0)	1.5 (0.6–2.1)	NS
Extra-articular disease (%)	25 (73.5%)	244 (66.7%)	NS
Depression n (%)	8 (23.5%)	63 (17.2%)	NS
Medication			
DMARDs n (%)	22 (64.7%)	205 (56%)	NS
MTX n (%)	33 (97.1%)	277 (75.7%)	0.001
Anti-TNF-α n (%)	4 (12%)	42 (11.5%)	NS
leflunomide n (%)	0 (0%)	16 (4.4%)	NS
prednisolone n (%)	13 (38.2%)	118 (32.2%)	NS
NSAIDs n (%)	7 (20.6%)	72 (19.7%)	NS
Cholesterol-lowering n (%)	6 (17.6%)	72 (19.7%)	NS

Results expressed as number (percentages), median (interquartile range) or mean ± SD as appropriate. RA+RC: patients with rheumatoid cachexia; RA-RC: patients without rheumatoid cachexia; P: level of significance; NS: non significant; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; TNF-α: tumour necrosis factor alpha; HAQ: Health Assessment Questionnaire; DMARDs: disease modifying anti rheumatic drugs; MTX: methotrexate; NSAIDs: non-steroidal anti-inflammatory drugs.

As expected, FFMI was significantly reduced in RA+RC compared to RA-RC (14.2±1.5 *vs*. 17.9±2.4 kg, $p<0.001$) while this was not the case for FMI (RA+RC *vs*. RA-RC: 12.1±3.2 *vs*. 13.5±3.8 kg, $p>0.05$). Albumin levels were significantly lower in RC+RA than RA-RC (39.6±6.7 *vs*. 42.4±4.9 g/L, p=0.001).

Classical CVD risk factors:

A non-significantly larger proportion of RA+RC patients were current smokers (*i.e*. smokers at the time of the assessment) compared to RA-RC (Table I). Systolic blood pressure was not significantly different between the two groups, but RA+RC had significantly lower diastolic blood pressure (73.3±10.8 mmHg) than RA-RC (79.4±11.1 mmHg) (p=0.003). No significant differences ($p>0.05$) were detected in any of the lipid assessments (RA+RC *vs*. RA-RC: triglycerides = 1.3(1.0–1.6) *vs*. 1.2 (0.9–1.6), total cholesterol=5.5(4.8–6.3) *vs*. 5.2(4.4–5.8) and LDL=3.1±1.3 *vs*. 3.0±1.2), or insulin resistance assessed via the homeostatic model assessment (RA+RC *vs*. RA-RC: 1.6(0.9–2.6) *vs*. 1.9(1.1–3.2)).

Novel CVD risk factors:

No significant differences were detected in any of the novel CVD risk factors studied: RA+RC *vs*. RA-RC: Type I plasminogen activator inhibitor antigen (28.0(25.9–46.6) *vs*. 28.4(18.0–40.5) ng/ml), tissue-type plasminogen

activator antigen (11.5(9.9–13.7) *vs*. 9.4(7.7–13.0) ng/ml), homocysteine (10.3(9.3–15.5) *vs*. 11.4(9.0–14.2) μmo/l), apolipoprotein B (1.0(0.7–1.1) *vs*. 0.9(0.7–1.1) μmol/l), serum uric acid (288.5(241.2–358.5) *vs*. 298.0(247.0–367.0) μmol/l), haemoglobin (13.4(12.3–14.2) *vs*. 13.2(12.3–14.2) g/dl), white cell count (7.3(5.4–8.9) *vs*. 7.4(6.1–9.3) x109/L), fibrinogen (4.3(3.5–5.1) *vs*. 4.4(3.7–4.9) g/dl) and von Willebrand Factor (113(11.6.5–169.5) *vs*. 130.6(96.8156.1) lU/dl); all $p>0.05$.

10-year CVD probability:
No significant difference ($p>0.05$) was detected in the 10-year CVD risk between the groups: RA+RC=5.0%(3.5–10.0) *vs*. RA-RC=5.0%(2.0–10.0).

Prevalent CVD and death:
Results are reported in number (percent). There were no significant differences in the prevalence of angina (2(5.9%) *vs*. 35(9.6%)), coronary artery bypass grafting (1(2.9%) *vs*. 9(2.5%)), heart attack (3(8.8%) vs. 25(6.8%)), peripheral vascular disease (2(5.9%) *vs*. 11(3.0%)), cardiac rhythm disease (1(2.9%) *vs*. 21(5.7%)), stroke (3(8.8%) *vs*. 14(3.8%)) or valve problems (1(2.9%) *vs*. 8(2.2%)) in RA+RC *vs*. RA-RC, respectively. During a follow-up period of 3 years, there was no significant difference either in all cause or CVD mortality between the two groups (RA+RC *vs*. RA-RC: 6.0% *vs*. 6.8% or 0% *vs*. 2.2), respectively.

Discussion

To the best of our knowledge, this is the first study directly investigating the cardiovascular profile of RA patients with RC. The results suggest that the presence of RC is not associated with worse classical or novel CVD risk factor profile, 10-year CVD risk, increased mortality or CVD prevalence.

Our findings are opposed to the statement that RC+RA is associated with increased CVD risk (9). This lack of association may be explained by the fact that the only published criteria for RC, as adopted in this study, are very stringent; this has resulted in a sample of RC+RA patients that had, in general, decreased body mass, but similar fat mass, in comparison with what is normally seen in RA (e.g. mean BMI of the present total cohort was ~28 kg/m^2). As such, the present RC criteria (being age- but not weight-related (12)) do not take into account overweight and obese patients; these may experience RC as well as increased CVD risk due to the increased prevalence of insulin resistance or worse adipokine profile (13, 14). It is also possible that due to the increased mortality of cachectic patients, the severely cachetic RA patients may have already died before inclusion in the cohort. This may be further supported by the fact that no difference was found either in all-cause or CVD mortality between RA+RC and RA-RC in this cohort over a follow-up period of three years exceeding 1500 patient years.

The potential link between RC and CVD has been previously highlighted (9) but never before investigated *per se*. This, however, is an important topic to explore since the increased fat deposition that masks the enhanced protein catabolism as a result of RC (3), could lead an adverse cardiovascular profile (15). Our data suggest this may not be the case, since, interestingly, the present RA+RC patients had similar body fat with the RA-RC patients despite the fact that their BMI was significantly lower.

In our study, RC prevalence was 10%, which is identical to that reported by Morley *et al*. (16), who also used a stringent approach for the diagnosis of RC. Using the present published criteria, the BMI of the RA+RC population is normal as opposed to the remaining non-cachectic population which is characterised as obese. Hence, the present findings are in line with published data that underweight and obese RA patients have worse disease manifestations (17). It is, however, very important to highlight, that to date, there are no uniform criteria for the definition of RC and most of the studies investigating the prevalence of RC have used different criteria (18). Hence, the statement that RC occurs in 2/3 of the RA population (9), is likely to be inaccurate and needs to be reconsidered.

In the present study, we adopted recent reference cut-off points for FFMI and FMI assessed by bioelectrical impedance (12), because this method has been consistently used in RA. We are aware that this method has its own disadvantages and needs further validation in RA (4) but it is based on more sound scientific methodology compared to previously adopted methods (18) and thus, provides a better prediction of overall fat and fat-free mass content (19). The fact that our RA+RC patients had significantly lower albumin may further support that they were experiencing enhanced catabolism.

This study is the first to show that, using the present strict criteria for RC, this metabolic abnormality does not appear to associate with worse cardiovascular profile in RA patients. This needs to be confirmed in long-term prospective studies.

References

1. METSIOS GS, STAVROPOULOS-KALINGLOU A, PANOULAS VF, KOUTEDAKIS Y, KITAS GD: Metabolism in patients with rheumatoid arthritis: resting energy expenditure, physical activity and diet-induced thermogenesis. Invited review. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery* 2008; 2: 97-102.
2. METSIOSGS,STAVROPOULOS-KALINOGLOU A, PANOULAS VF *et al*.: New resting energy expenditure prediction equations for patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2008; 47: 500-6.
3. ROUBENOFF R, ROUBENOFF RA, CANNON JG *et al*.: Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. *J Clin Invest* 1994; 93: 2379-86.
4. STAVROPOULOS-KALINOGLOU A, METSIOS GS, KOUTEDAKIS Y *et al*.: Redefining overweight and obesity in rheumatoid arthritis patients. *Ann Rheum Dis* 2007; 66: 1316-21.
5. MARCORA S, LEMMEY A, MADDISON P: Dietary treatment of rheumatoid cachexia with beta-hydroxy-beta-methylbutyrate, glutamine and arginine: a randomised controlled trial. *Clin Nutr* 2005; 24: 442-54.
6. MARCORA SM, LEMMEY AB, MADDISON PJ: Can progressive resistance training reverse cachexia in patients with rheumatoid arthritis? Results of a pilot study. *J Rheumatol* 2005; 32: 1031-9.
7. METSIOSGS,STAVROPOULOS-KALINOGLOU A, DOUGLAS KM *et al*.: Blockade of tumour necrosis factor-alpha in rheumatoid arthritis: effects on components of rheumatoid cachexia. *Rheumatology* (Oxford) 2007; 46: 1824-7.
8. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, BERJA A *et al*.: Anti-tumour necrosis factor

alpha therapy modulates ghrelin in patients with severe rheumatoid arthritis. *Ann Rheum Dis* 2008; 67: 1644-6.
9. WALSMITH J ROUBENOFF R: Cachexia in rheumatoid arthritis. *Int J Cardiol* 2002; 85: 89-99.
10. PANOULAS VF, DOUGLAS KM, MILIONIS HJ *et al*.: Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2007; 46: 1477-82.
11. ENGVALL IL, ELKAN AC, TENGSTRAND B, CEDERHOLM T, BRISMAR K, HAFSTROM I: Cachexia in rheumatoid arthritis is associated with inflammatory activity, physical disability, and low bioavailable insulin-like growth factor. *Scand J Rheumatol* 2008; 37: 321-8.
12. SCHUTZ Y, KYLE UU, PICHARD C: Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y. *Int J Obes Relat Metab Disord* 2002; 26: 953-60.
13. GONZALEZ-GAY MA, LLORCA J, GARCIA-UNZUETA MT *et al*.: High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 596-603.
14. ANTUNA-PUENTE B, FEVE B, FELLAHI S, BASTARD JP: Adipokines: the missing link between insulin resistance and obesity. *Diabetes Metab* 2008; 34: 2-11.
15. STAVROPOULOS-KALINOGLOU A, METSIOS GS, PANOULAS VF *et al*.: Associations of obesity with modifiable risk factors for the development of cardiovascular disease in patients with rheumatoid arthritis. *Ann Rheum Dis* 2009; 68: 242-5.
16. MORLEY JE, THOMAS DR, WILSON MM: Cachexia: pathophysiology and clinical relevance. *Am J Clin Nutr* 2006; 83: 735-43.
17. STAVROPOULOS-KALINOGLOU A, METSIOS GS, PANOULAS VF *et al*.: Underweight and obese states both associate with worse disease activity and physical function in patients with established rheumatoid arthritis. *Clin Rheumatol* 2008;
18. SUMMERS GD, DEIGHTON CM, RENNIE MJ, BOOTH AH: Rheumatoid cachexia: a clinical perspective. *Rheumatology* (Oxford) 2008; 47: 1124-31.
19. HEITMANN BL, KONDRUP J, ENGELHART M *et al*.:Changes in fat free mass in overweight patients with rheumatoid arthritis on a weight reducing regimen. A comparison of eight different body composition methods. *Int J Obes Relat Metab Disord* 1994; 18: 812-9.