Tight control of disease activity fails to improve body composition or physical function in rheumatoid arthritis patients

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Short title: Effects of T2T on body composition and function in RA

Abstract

Objective. RA typically features "rheumatoid cachexia" (loss of muscle mass (MM) and excessive fat mass (FM), especially trunk FM), which contributes to physical disability. Since rheumatoid cachexia is driven by inflammation, it would be anticipated that the success of tight control of disease activity, such as "treat-to-target" (T2T), in attenuating inflammation would benefit body composition and physical function. This cross-sectional study assessed the impact of T2T on body composition and objectively-assessed function in RA patients.

Methods. Eighty-two RA patients exclusively treated by T2T, were compared to 85 matched sedentary healthy controls (HC). Body composition was estimated by DXA, with appendicular lean mass (ALM) the surrogate measure of total MM. Physical function was assessed by knee extensor strength, handgrip strength, 30s sit-to-stands, 8' up & go, and 50' walk (tests which reflect the ability to perform ADLs).

Results. Although generally well treated (mean DAS28=2.8, with 49 % in 'remission'), RA patients had ~10% proportionally less ALM and were considerably fatter (by ~27%), particularly in the trunk (~32%), than HC's. All measures of function were 24-34% poorer in the RA patients relative to HC.

Conclusions. Despite marked improvements in disease control (most patients achieving or approaching 'remission'), the relative loss of MM and increased adiposity in RA patients compared to matched-HC is similar to that observed pre-T2T. Additionally, performance of objective function tests is unchanged from that reported by our group for pre-T2T RA patients. Thus T2T, even in responsive RA patients, has not attenuated rheumatoid cachexia or improved objectively-assessed function.

(249 words)

Key words: rheumatoid arthritis, treat-to-target, rheumatoid cachexia, body composition, physical function

Rheumatology key messages

- T2T RA patients still show significant muscle loss, exacerbated adiposity and substantially impaired physical function.
- Patients responding to T2T typically have the physical function of healthy individuals 25 years older.
- By concentrating on DAS28, T2T protocols may distract rheumatologists' attention from physical function.

INTRODUCTION

Rheumatoid arthritis (RA) is characterised by adverse changes in body composition (i.e. reduced muscle mass and increased adiposity) termed 'rheumatoid cachexia' [1]. Although prevalence of this condition varies according to measurement method and definition employed, muscle loss of 7.4-14.0% relative to matched healthy controls [2-5] are observed in approximately 67% of stable RA patients [3, 6-15] whilst obesity, determined by body composition, is present in around 80% of stable patients [3, 9-12, 16], with trunk adiposity especially prevalent [3, 8, 9-12, 17-18]. These changes in body composition, as well as exacerbating mortality and co-morbidity risk [15-19], also contribute significantly to disability [7, 20-22].

In recent years, individually tailored treatment strategies featuring early and aggressive DMARD use and frequent monitoring of treatment response to achieve low disease activity, preferably 'clinical remission', have been the cornerstone of pharmacologic treatment of RA. This approach, best exemplified by 'treat-to-target' (T2T) [23-24], has been shown to be substantially better in controlling inflammation and arresting progression of joint damage than previous treatment strategies [23-26]. Given that rheumatoid cachexia is thought to be driven by disease activity (DA), and inflammation in particular [3, 14-15, 27], it would be anticipated that the tighter control of DA/inflammation achieved by T2T would attenuate rheumatoid cachexia and, as a consequence, reduce functional limitations in RA patients. Pertinently, restoration of functional ability is an explicit aim of both EULAR and ACR recommendations for T2T [23-24, 28]. Although studies assessing body composition in RA patients have been performed since the widespread use of T2T (~2008), these studies [4, 6, 8, 10, 18, 20, 29-31] have either exclusively or primarily used patients who commenced treatment years prior to the adoption of T2T, and therefore do not inform on the effects on body composition of T2T *per se*. Additionally, investigations into the impact of T2T on physical function have only used subjective instruments such as the Health Assessment Questionnaire (HAQ) [26, 32-33]. However, these

measures are strongly influenced by pain [34-35], which diminishes with T2T, and are often insensitive to changes in function in patients with controlled disease [9, 36].

Thus, we aimed to determine whether the adverse effects of RA on body composition and physical function still exist in this era of tight control of DA. To this end, we compared body composition and objectively-assessed physical function of RA patients treated exclusively by T2T with that of age- and sex-matched healthy sedentary controls (HC). Additionally, we compared our current findings with those previously reported by our group for stable RA patients (i.e. studies performed either before local adoption of T2T, or, if more recent, on patients who commenced treatment pre-T2T [3-4, 9-12, 30]). Lastly, this investigation sought to further examine the time-courses of rheumatoid cachexia and RA disability.

METHODS

This cross-sectional study was conducted between February 2013 and March 2015, with approval from the North Wales Research Ethics Committee – West (12/WA/0323), and in compliance with the Helsinki Declaration.

Study population

RA patients with stable disease were recruited from outpatient clinics of the Peter Maddison Rheumatology Centre (PMRC), North Wales. For inclusion, participants had to: (a) fulfil the ACR 2010 revised criteria for RA [37]; (b) be aged ≥ 18 years; (c) not be cognitively impaired; (d) be free of other cachectic diseases or conditions preventing safe participation; (e) not be taking anabolic drugs or nutritional supplements; and (f) not be pregnant. Only patients who commenced DMARD treatment following the PMRC's adoption of treatment strategies in-line with the T2T recommendations of Smolen et al [23] (i.e. post 1/1/2008) were included. Once recruited, participants were categorised

into either ‘recent-onset’ (≤ 12 months since diagnosis) or ‘established’ (> 12 months since diagnosis) disease cohorts.

For comparison, sedentary age- and sex-matched HC were recruited from the local community. To be eligible for the study, HC must have satisfied all of the inclusion criteria for RA patients, except for the diagnosis of RA.

Assessments and outcome measures

Participants presented for assessments in an overnight fasted state.

Anthropometric and body composition measures

Routine anthropometric measures (body mass (BM), height, and waist and hip circumferences) were performed using standard procedures.

Total and regional lean, fat, and bone masses were estimated using a whole body fan-beam DXA scanner (Hologic, QDR Discovery 45615, software V12.4), with appendicular lean mass (ALM) used as a surrogate measure of total body muscle mass [3]. The in-house co-efficient of variation (CV) of 1.4% of our scanner complies with manufacturer’s guidelines.

Objective physical function

Maximal isometric knee extensor strength (IKES) was measured using an isokinetic dynamometer (Humac Cybex Norm 2004, Computer Sports Medicine Inc., Massachusetts, USA) and maximal handgrip strength (HGS) by a Grip-A dynamometer (Takei Kiki Kogyo, Japan) using previously described protocols [3]. Three objective function tests, specifically developed to evaluate the capacity of older adults to perform activities of daily living (ADL [38]): ‘sit-to-stands in 30 seconds’ (STS-30),

145 '8-foot up and go' (8'UG) and '50-foot walk' (50'W) tests), were also assessed. Performance of each
146 of these strength and function tests, which are routinely used by our group [3-4, 9-12, 30-31, 39], was
147 preceded by a submaximal practice.
148
149 *Clinical measures.* Disease activity was assessed by the Disease Activity Score in 28 joints (DAS28)
150 using C-reactive protein (CRP), with 'remission' defined as DAS28 < 2.6. Physical disability was
151 subjectively evaluated by the Multidimensional HAQ (MDHAQ [40]).
152
153 **Statistical analysis**
154 The primary outcome was ALM normalised for BM (ALM %), as this is the LM measure most relevant
155 to performing ADL (i.e. comparing absolute ALM ignores disparities in BM and the effect fat mass
156 (FM) has on performing ADL). The secondary outcomes included other aspects of body composition
157 (total LM, total FM, trunk FM, and % body fat (BF%)) and the objective physical function measures.
158
159 The primary statistical analyses involved comparison of the RA group versus the HC group, followed
160 by sub-analyses of: 'recent-onset' versus 'established' RA patients; RA patients who, at the time of
161 testing, had achieved clinical remission versus patients who had not; 'remission' patients versus HC;
162 and finally, informal comparison of current results with our 'historic', pre-T2T data [3-4, 9-12, 30-31;
163 patients for these studies generally commenced treatment 1992-2004]. Statistical analysis involved
164 multiple (MANOVA) or univariate analysis of variance (ANOVA) according to appropriateness, and
165 Chi-squared tests were used for comparison of dichotomous variables. Significance was set at $P < 0.05$
166 and a trend recognised as $P = 0.05$ - 0.10. Data is presented as mean (±SD).
167
168 **RESULTS**
169 One hundred and ninety-seven (n = 197) patients with RA were deemed eligible for the study and

approached. Of these, 115 (58%) declined participation (primarily due to: 'not interested' or time and/or travel constraints) leaving 82 patients who were recruited. At the time of assessment, 33 of these 82 patients had been diagnosed ≤ 12 months previously ('recent-onset' group; mean disease duration ~7 months), whilst the remaining 49 had a disease duration of 1-7 years ('established' group; mean duration ~2 years 11 months). Eighty-five age- and sex-matched sedentary HC participants were also recruited.

Demographic and clinical characteristics

Table 1 displays the demographic and clinical characteristics of the 82 RA patients and 85 HC participants. These groups were precisely matched for mean age ($P = 0.962$) and gender distribution ($P = 0.992$). RA patients were more frequently current ($P < 0.001$) or former ($P < 0.001$) smokers, and generally were more sedentary ($P < 0.001$) than the HC. For patients, the mean DAS28 score was 2.8, indicating generally 'low DA', and 49% had achieved a current state of 'clinical remission'. DMARD treatment is summarised in Table 1.

No differences in demographic or clinical characteristics were identified between the 'recent-onset' or 'established' RA patients (data not shown), with the exception of disease duration and the proportion on combination therapy (7.1 ± 3.0 vs 34.7 ± 17.0 months, $P < 0.001$; and 16/33 (48%) vs 14/49 (29%), $P = 0.066$, respectively). Similarly, no differences for demographic or clinical characteristics were evident between seropositive and seronegative patients (data not shown: P's 0.625-0.905).

Anthropometry and body composition

Anthropometric and DXA-assessed body composition data appear in Table 2. Despite being shorter (mean ~3cm, $P = 0.019$), RA patients were heavier (mean BM: +4.8 kg, $P = 0.093$), and consequently

194 their mean BMI higher ($P = 0.002$), than HC. RA patients also had a greater mean waist circumference
195 (+7.7 cm, $P = 0.001$) and waist:hip ratio ($P < 0.001$) than HC.
196
197 When adjusted for BM (i.e. % of), RA patients had ~10% less muscle than HC (ALM %, $P < 0.001$).
198 This relative deficit corresponds with the proportional loss of ALM we observed in stable RA patients,
199 of similar age and gender distribution, who had commenced treatment ~1992-2004 (i.e. ~9%, RA n =
200 23, matched HC, n = 23 [4]; ~11%, RA n = 20, matched HC, n = 20 [3]). When expressed absolutely
201 (kg), RA patients in the current study exhibited less ALM (-1.1 kg) and TLM (-0.8 kg) than the HC,
202 although these differences were not statistically significant.
203
204 DXA-assessed body composition confirmed that RA patients were considerably fatter than HC, with
205 the group differences in BM more than accounted for by higher total FM in patients (+5.4 kg, 26.5%
206 greater, $P < 0.001$). Consequently, BF% was also higher in patients ($P < 0.001$). As anticipated, the
207 majority of this increased adiposity was situated on the trunk (+3.2 kg, 32.3% higher than HC, $P =$
208 0.001). In pre-T2T patients we had noted mean increases in total FM of ~17% [4] and ~13% [3] relative
209 to HC.
210
211 No differences in anthropometric or DXA measures were evident between the 'recent-onset' and
212 'established', or between seropositive and seronegative, RA patients (data not shown; P's = 0.581-
213 0.998).
214
215 ***Objective physical function***
216 Compared with HC, RA patients performed poorly in each of the objective function measures (Table
217 3): IKES was 24.3% less ($P < 0.001$); HGS, 25.3% less ($P < 0.001$); STS-30, 34.2% less ($P < 0.001$);
218 8'UG, 31.1% slower ($P < 0.001$); and 50'W, 28.0% slower ($P < 0.001$). The absolute levels of

performance for those tests not subject to equipment changes (i.e. STS-30, 8'UG, 50' W), achieved by RA patients in the current study are not an improvement on those we observed in stable pre-T2T RA patients (STS-30: mean range 10.9 – 14.7 repetitions, overall mean = 12.4 (vs 12.0 repetitions in the current study) [3-4, 9-12, 30-31]; 8'UG: mean range 6.0 – 6.4 secs, overall mean = 6.2 (vs 7.4 secs) [4, 30-31]; 50'W mean range 9.1 – 10.0 secs, overall mean = 9.5 (vs 10.7 secs) [4, 9-10, 30-31].

As with the anthropometric and body composition measures, there were no differences in performance for any of the objective function tests between the 'recent-onset' and 'established' RA patients (data not shown; *P*'s = 0.435-0.778).

Subjective measures of disability and health

As expected, RA patients had higher MDHAQ scores than the HC group (*P* = 0.001; Table 1). Despite the marked impairments in objectively-assessed physical function relative to HC, the RA patients subjectively regarded themselves as only 'mildly disabled' (Table 1). There was no difference in MDHAQ scores between 'recent-onset' and 'established' RA patients (data not shown, *P* = 0.880).

'Remission' versus 'non-remission' RA patients

Of the 82 RA patients, 40 had achieved clinical remission at the time of assessment (DAS28: 2.0 ± 0.4). There were no differences in age, seropositivity, disease duration or medication between 'remission' and 'non-remission' patients, however, proportionally fewer females achieved 'remission' (58% vs 71%, *P* = 0.187) (Table 4).

In comparison to those not in remission (DAS28: 3.6 ± 0.8), the 'remission' patients generally had slightly better body composition, albeit not significantly (Table 5), and performed the function tests better (Table 6). However, even in this subgroup of highly responsive patients, body composition (i.e.

waist circumference, $P = 0.039$; waist:hip ratio, $P < 0.001$; ALM, $P = 0.003$; ALM%, $P < 0.001$; total FM, $P = 0.014$; BF%, $P = 0.001$; trunk FM, $P = 0.017$) and objectively-assessed function (relative deficits of 13 – 31%; IKES, $P = 0.002$; HGS, $P < 0.001$; STS-30, $P < 0.001$; 8'UG, $P = 0.008$; 50'W, $P = 0.014$) were still much worse than for HC.

DISCUSSION

This is the first investigation of the effects on body composition and objectively-assessed physical function of current treatment regimens which aim to tightly control DA in RA patients. Overall the findings show that our T2T RA patients, including those who have achieved clinical remission, continue to have substantially reduced muscle mass, much greater levels of adiposity (especially trunk), and considerably worse function than sedentary age- and sex-matched healthy individuals. These adverse effects are despite a mean DAS28 of 2.8 (an 'acceptable alternative therapeutic goal' [23-24]) and achievement of 'clinical remission' in approximately half our patients, both of which indicate that our cohort is well-treated and generally benefiting from the T2T approach.

Whilst the precise mechanisms underlying rheumatoid cachexia remain unclear, disease activity (i.e. inflammation) is widely accepted to be the primary driver [1, 13, 27, 29, 41]. Hence, it would be anticipated that the success of T2T in suppressing inflammation would be reflected in improved body composition in RA patients treated exclusively by this strategy relative to patients who received earlier, less clinically effective treatments. However, the proportional loss of muscle mass of ~10 % observed in our current patients relative to matched, sedentary healthy controls is similar to what we had noted in stable, pre-T2T RA patients (~9%, for patients with a mean RA Disease Activity Index (RADAI) = 3.1 ± 0.3 [4]; and ~11%, for patients with RADAI = 2.65 ± 1.4 [3]). This current deficit is also in line with the DXA-assessed ALM/BM% differences between controlled pre-T2T patients and healthy individuals described by others; i.e. 12% [5], 8% [42], 9% [43] (data collection 2004-

2006), 11% in women and 10% in men [2] (RA patients diagnosed 1995-2001) and in the follow-up to the last study, 11% in women and 7% in men [44]. Additionally, Elkan et al [7] (data collection 2004-2005) found an 11% reduction in DXA-assessed fat free mass index (FFM/height $(m)^2$) of RA patients with active disease (mean DAS28 = 5.5) versus a matched European reference population.

The elevated adiposity we observed in our T2T RA patients relative to sedentary controls (FM (kg) increased by 26.5%, BF% increased 15.5%, trunk FM increased 32.3%) is also consistent with the observations made in our pre-T2T RA patients (total FM increases of ~17% [4] and ~13% [3] versus HC), and generally with the DXA-assessed disparities in adiposity reported by others in stable, pre-T2T RA patients relative to matched HC (FM (kg) increased by 12% [5]; FM and trunk FM increased 13% and 25%, respectively [43]; FM and trunk FM increased 12.5% and 13.5% in females, and 5.4% and 7.1% in males, respectively [42]; FM and trunk FM increased 13.5% and 21.6%, respectively, in females, with no additional adiposity in males [2]; and FM and trunk FM increased 15.3% and 19.4%, respectively, in females, with no additional adiposity in males [44]). Whilst the RA patients in the current study were more sedentary than the HC, the between-group difference only amounted to approximately 30 minutes walking/week, and both groups fall well short of the minimum recommendation for long-term loss of FM of 250 min/week of moderate intensity physical activity (PA) [45]. This 30 minute disparity in low-moderate intensity PA would also not account for the difference in MM, as higher-intensity exercise is required to elicit hypertrophy [45]. Thus, our findings clearly indicate that rheumatoid cachexia has not been resolved, or even attenuated, by tight control of DA, despite the other clinical benefits this approach confers.

We also demonstrated in this study that objectively-assessed physical function has not improved with T2T therapy. This finding is not surprising in view of the lack of improvement in either muscle or fat masses, and the strong association between these and physical function in RA patients [16, 20-

294 22]. In our T2T patients, strength relative to health controls was reduced by ~25% and the
295 performance level of tests designed to reflect the ability to perform ADL and live independently [38],
296 reduced by about a third. More tellingly with regard to the effect of T2T on function, the test scores
297 obtained by patients in the current study were not better, and in some cases were worse (8'UG,
298 50'W), than those of patients in our earlier studies [3-4, 9-12, 30-31] who were of similar age and
299 gender distribution. To provide a context of how poor the physical function of our T2T RA patients
300 is, Rikli and Jones [38] recently published minimal fitness standards compatible with living
301 independently late in life using objective tests (including STS-30 and 8'UG). In the present study,
302 the RA women (mean age 58.6 years) achieved a STS-30 score appropriate for healthy 'moderate
303 functioning' women aged 80-84 years, and the RA men (mean age of 65.0 years) a score in line with
304 healthy 'moderate functioning' men of 85-89 years. For the 8'UG test, the respective equivalents
305 were 85-89 years for the women, and the men failed to achieve the standard of 90-94 year old
306 healthy men (the highest age category). Hence, on average, both the female and male patients had
307 the function of healthy individuals approximately 25 years older.
308
309 Despite the substantial deficits in objectively-measured physical function (28-34% worse than
310 sedentary HC), it is revealing that the patients generally rated their disability as only being 'mild'
311 (mean MDHAQ = 0.57). Also of interest, is that our earlier (pre-T2T) patients, although generally
312 performing the objective tests as well, if not better than, the recent T2T patients, subjectively rated
313 their disability as being higher (e.g. data collected 2005-2007, baseline means; DAS28 = 3.3, STS30
314 = 12.5 reps, 50'W = 9.3 secs, IKES = 323 N, MDHAQ = 0.91 [9]). This improvement in
315 subjectively-assessed function (e.g. HAQ, MDHAQ) with T2T has been widely reported [26, 32-33]
316 and may be due to reductions in pain [25], as pain is known to strongly influence HAQ scores [34-
317 35, 46]. This discord between objectively- and subjectively-assessed function in stable RA patients,
318 together with the underestimation RA patients have of their disability, highlights the value of

objective function tests and provides further evidence of their greater sensitivity for detecting functional change in patients with well-controlled disease [9, 36].

A key aim of T2T is "normalisation of function" (e.g. "Overarching principal" B; EULAR/International Task Force Recommendations [23-24]; ACR [28]). Our findings indicate that T2T has made inadequate progress in achieving this, even for patients achieving 'remission' (DAS28 = 2.0 ± 0.4; whose performance of function tests was approximately $1/5^{th}$ – $1/3^{rd}$ poorer than sedentary HC). Additionally, we may have underestimated the extent of functional loss (and the perturbations in body composition) existing in broader RA populations as low DA and a high remission rate were achieved for our patients primarily with DMARD monotherapy, and no recourse to biologics, indicating that our cohort generally has mild-moderate, and responsive, disease.

Another point to raise is the failure of widely-used measures of treatment efficacy for T2T (e.g. DAS28) to assess function, either objectively or subjectively, which is counter to both the prominence that restoration of physical function has amongst the goals of this treatment, and the strong associations function has with morbidity, mortality, treatment costs and patient quality of life in RA [47].

An obvious question arising from our results is why has T2T failed to improve body composition and, consequently, physical function, given its beneficial effects on inflammation and DA, the purported drivers of rheumatoid cachexia? A likely explanation is that the perturbations in body composition predominantly occur very early in the disease (i.e. during the 'pre-clinical' stage), and thus prior to the initiation of treatment. This proposal is consistent with: i) the absence of differences in anthropometric, body composition, or physical function measures between our 'recent' and 'established' RA patients; ii) reports of a similar incidence and magnitude of rheumatoid cachexia in recently diagnosed RA

patients as for established patients [2, 12]; iii) indications that the rate of muscle loss in established, controlled patients is similar to that of healthy individuals [10, 44]; and iv) the consistent findings that disease processes, including inflammation and co-morbidity risk are already elevated in the pre-clinical period [48].

To summarise, our study shows that T2T, despite its enhanced efficacy in reducing DA, inflammation and joint damage, has not improved patients' body composition or physical function relative to previous treatment regimens. As a consequence, RA patients remain significantly muscle wasted and fatter, and this, at least in part, accounts for why they have substantially impaired function relative to healthy individuals. Unfortunately, these important adverse consequences of RA are usually neglected as the T2T regimen posits that DAS28 score should be the clinician's primary concern. Consequently, in this pharmacological model of treatment, focus on the need for rehabilitation has diminished. The inclusion of an objective function test(s) during clinical reviews of DA would highlight to both the rheumatologist and the patient the need for adjunct treatments, such as high intensity exercise (especially resistance training [3, 9] and nutritional supplementation [11, 49-50], that specifically aim to restore body composition and physical function in RA patients.

Words: 3495

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551 **TABLE 1. Demographic and clinical characteristics for rheumatoid arthritis patients and**

552 **sedentary, age- and sex-matched health controls**

	RA (*n* = 82)	HC (*n* = 85)	*P*
Age (years)	60.9 (±11.7)	60.9 (±8.1)	0.962
Sex (*n* female) (%)	53 (65)	55 (65)	0.992
Disease duration (months)	23.8 (±19.0)	-	-
Seropositive RA; *n* (%)	67 (85)	-	-
DAS28 (0-10)	2.8 (1.0)	-	-
Medications, n (%)			
Methotrexate [a]	68 (83)	-	-
Hydroxychloroquine	26 (32)	-	-
Leflunomide	7 (9)	-	-
Sulfasalazine	5 (6)	-	-
Tacrolimus	3 (4)	-	-
Mycophenolate mofetil	1 (1)		
Biologic	0 (0)	-	-
Mono-DMARD therapy	48 (59)		
Combination DMARDs [b]	30 (37)	-	-
No DMARD	3 (4)		
Corticosteroids [c]	7 (9)	1[d] (1)	**0.026***
Analgesics/NSAIDs	44 (54)	8 (9)	< **0.001***
Smoking status, n (%)			
Current smokers; *n* (%)	18 (22)	3 (5)	< **0.001***
Ex-smokers; *n* (%)	39 (48)	25 (31)	< **0.016***
Never smokers; *n* (%)	25 (30)	52 (61)	< **0.001***

Subjective measure of disability			
MDHAQ score (/3)	0.57 (±0.54)	0.08 (±0.24)	**0.001***
Exercise frequency [e], n (%)			
Exercise frequency score (0-3)	1.1 (±1.3)	2.2 (±1.0)	< **0.001***
Do not regularly exercise (0)	43 (52)	9 (11)	< **0.001***
1-2 times a month (1)	6 (8)	7 (8)	0.825
1-2 times a week (2)	11 (14)	27 (32)	**0.005***
>3 times a week (3)	20 (25)	41 (49)	**0.001***

Unless stated, data presented as mean (±SD). Differences at baseline were assessed using analyses of variance or Chi-square test as appropriate. RA = rheumatoid arthritis; HC = healthy control group; Seropositive RA = rheumatoid factor and/or anti-CCP seropositive; DAS28 = Disease Activity Score in 28 joints; [a] = supplemented with folate; DMARD = disease modifying anti-rheumatic drug; [b] = double or triple DMARD therapy; [c] = current corticosteroid range 5.0 – 10.0 mg/d; [d] = corticosteroid inhaler for asthma; NSAID = non-steroidal anti-inflammatory drug; MDHAQ = multi-dimensional health assessment questionnaire; [e] = self-reported exercise frequency taken from MDHAQ (not reported: RA = 2, HC = 1); Exercise frequency score: 0 = no regular exercise; 1 = 1-2 times a month; 2 = 1-2 times a week; 3 = >3 times a week; unless adjusted by Bonferroni adjustment * = significant ($P < 0.05$).

TABLE 2. Body composition measures for rheumatoid arthritis patients and sedentary, age- and sex-matched health controls

	RA (n = 82)	HC (n = 85)	% difference (CI for absolute difference)	P
Waist circ. (cm)	91.6 (±17.9)	83.9 (±10.8)	↑ 8.4 (3.2 – 12.2)	**0.001***
Hip circ. (cm)	101.9 (±12.7)	99.1 (±7.8)	↑ 2.7 (-0.4 – 6.1)	0.128
Waist: hip ratio	0.90 (±0.10)	0.85 (±0.08)	↑ 5.6 (0.0 – 0.1)	< **0.001***
BM (kg)	76.5 (17.9)	71.7 (±11.1)	↑ 6.3 (0.2 – 9.3)	0.093[#]
Height (cm)	165.1 (±7.9)	168.1 (±8.6)	↓ 3.0 (0.5 – 5.5)	**0.019***
BMI (kg/m^2)	28.0 (±6.0)	25.4 (±3.4)	↑ 9.3 (-4.1 - -1.2)	**0.002***
DXA-assessed measures				
ALM (kg)	19.8 (±4.6)	20.9 (±5.2)	↓ 5.6 (-0.4 – 2.6)	0.158
ALM % (ALM/TBM %)	26.2 (±4.0)	28.8 (±4.2)	↓ 9.9 (1.4 – 3.9)	< **0.001***
Total LM (kg)	48.7 (±9.8)	49.5 (±10.0)	↓ 1.6 (-2.2 – 3.9)	0.578
TLM % (LM/BM %)	64.4 (±7.5)	68.6 (±6.8)	↓ 6.5 (1.9 – 6.3)	< **0.001***
Total FM (kg)	25.8 (±10.4)	20.4 (±6.2)	↑ 26.5 (-7.9 - -2.7)	< **0.001***
BF%	32.7 (±7.8)	28.3 (±7.2)	↑ 15.5 (2.1 – 6.7)	< **0.001***
Trunk FM (kg)	13.1 (±6.3)	9.9 (±3.7)	↑ 32.3 (1.6 – 4.8)	**0.001***

Data presented as mean (±SD). CI = 95 % confidence interval; RA = rheumatoid arthritis; HC = healthy control group; BM = body mass; BMI = body mass index; DXA = dual energy x-ray absorptiometry; ALM = appendicular lean mass; TLM = total lean mass; FM = fat mass; BF% = % body fat (i.e. FM/BM x 100); unless adjusted by Bonferroni adjustment * = significant (P < 0.05), [#] = trend (P = 0.05 - 0.10).

TABLE 3. Objective physical function and self-reported disability for rheumatoid arthritis patients and sedentary, age- and sex-matched health controls

	RA (n = 82)	HC (n = 85)	Absolute difference (*% difference*) (CI)	*P*
IKES (N)	380 (±140)	472 (±152)	↓ 92 *(24.3)* (46 – 138)	< **0.001***
HGS (kg)	26.5 (±8.8)	33.2 (±9.9)	↓ 6.7 *(25.3)* (3.8 – 9.7)	< **0.001***
STS-30 test (reps)	12.0 (±3.6)	16.1 (±4.3)	↓ 4.1 *(34.2)* (2.8 – 5.3)	< **0.001***
8'UG (secs)	7.4 (±3.9)	5.1 (±1.0)	↑ 2.3 *(31.1)* (1.4 – 3.1)	< **0.001***
50'W (secs)	10.7 (±5.3)	7.7 (±1.8)	↑ 3.0 *(28.0)* (1.8 – 4.3)	< **0.001***

Data presented as mean (±SD). CI = 95 % confidence interval; RA = rheumatoid arthritis; HC = healthy control group; IKES = isometric knee extensor strength; HGS = handgrip strength; STS-30 = Sit-to-stands in 30 seconds; 8'UG = 8-foot up and go; 50'W = 50-foot walk: unless adjusted by Bonferroni adjustment * = significant ($P < 0.05$).

597 **TABLE 4. Demographic and clinical characteristics for rheumatoid arthritis patients in 'remission' (DAS28 < 2.6) or not (DAS28 ≥ 2.6)**

	'In remission' vs 'Not in remission'			HC vs 'In remission'	
	'In remission' (*n* = 40)	'Not in remission' (*n* = 42)	*P*	HC (*n* = 85)	*P*
Age (years)	60.4 (±12.2)	61.4 (±11.3)	0.706	60.9 (±8.1)	0.764
Sex (*n* female) (%)	23 (58)	30 (71)	0.187	55 (65)	0.435
Disease duration (months)	23.1 (±17.5)	24.5 (±20.6)	0.740	-	-
Serpositive RA; *n* (%)	32 (80)	35 (83)	0.886	-	-
DAS28 (0-10)	2.0 (±0.4)	3.6 (±0.8)	**< 0.001***	-	-
CRP (mg/L)	7.3 (±7.7)	13.1 (±14.4)	**0.024***	-	-
Medications, n (%)					
Methotrexate [a]	34 (85)	34 (81)	0.626	-	-
Hydroxychloroquine	3 (8)	2 (5)	0.604	-	-
Leflunomide	3 (8)	4 (10)	0.743	-	-
Sulfasalazine	13 (33)	13 (31)	0.880	-	-
Tacrolimus	1 (3)	1 (2)	0.972	-	-
Mycophenolate mofetil	0 (0)	1 (2)	-	-	-
Biologic	0 (0)	0 (0)	-	-	-
Mono-DMARD therapy	24 (60)	25 (60)	0.930	-	-
Combination DMARDs [b]	15 (38)	15 (36)	0.930	-	-
No DMARD	1 (3)	2 (5)	0.586	-	-
Corticosteroids [c]	3 (8)	4 (10)	0.743	1 [d] (1)	**0.061***
Analgesics/NSAIDs	16 (40)	28 (67)	**0.015***	8 (9)	**< 0.001***

Smoking status, n (%)					
Current smokers; *n* (%)	7 (18)	11 (26)	0.180	3 (5)	**0.014***
Ex-smokers; *n* (%)	19 (48)	20 (48)	0.493	25 (31)	**0.007***
Never smokers; *n* (%)	14 (35)	11 (26)	0.542	52 (61)	**0.001***
Subjective measure of disability					
MDHAQ score (/3)	0.32 (±0.32)	0.81 (±0.59)	**< 0.001***	0.08 (±0.04)	**0.001***
Exercise frequency [e], n (%)					
Exercise frequency score (0-3)	1.1 (±1.3)	1.2 (±1.3)	0.733	2.2 (±1.0)	**< 0.001***
Do not exercise (0)	22 (55)	21 (50)	0.733	7 (8)	**< 0.001***
1-2 times a month (1)	4 (10)	2 (5)	0.363	7 (8)	0.745
1-2 times a week (2)	4 (10)	7 (18)	0.376	27 (32)	**0.009***
>3 times a week (3)	10 (25)	10 (25)	0.900	41 (49)	**0.014***

Unless stated, data presented as mean (±SD). Differences at baseline were assessed using analyses of variance or Chi-square test as appropriate. Seropositive RA = rheumatoid factor and/or anti-CCP seropositive; DAS28 = Disease Activity Score in 28 joints; [a] = supplemented with folate; DMARD = disease modifying anti-rheumatic drug; [b] = double or triple DMARD therapy; [c] = current corticosteroid range 5.0 – 10.0 mg/d; [d] = corticosteroid inhaler for asthma; NSAID = non-steroidal anti-inflammatory drug; MDHAQ = multi-dimensional health assessment questionnaire; [e] = self-reported exercise frequency taken from MDHAQ (not reported: RA = 2, HC = 1); Exercise frequency score: 0 = no regular exercise; 1 = 1-2 times a month; 2 = 1-2 times a week; 3 = >3 times a week; unless adjusted by Bonferroni adjustment * = significant ($P < 0.05$); [#] = trend ($P = 0.05$ - 0.10).

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607 **TABLE 5. Body composition measures for rheumatoid arthritis patients in 'remission' (DAS28 < 2.6) or not (DAS28 ≥ 2.6)**

	'In remission' vs 'Not in remission'					HC vs 'In remission'		
	'In remission' (n = 40)	'Not in remission' (n = 42)	Absolute difference (CI)	P	$P^{¥}$	HC (n = 85)	Absolute difference (CI)	$P^{¥}$
Waist circ. (cm)	90.3 (±16.5)	92.9 (±19.2)	-2.6 (-10.5 – 5.3)	0.514	0.258	83.9 (±10.8)	-6.4 (-10.7– - 0.3)	**0.039***
Hip circ. (cm)	100.0 (±10.0)	103.8 (±14.7)	-3.9 (-9.4 – 1.7)	0.169	0.246	99.1 (±7.8)	-0.9 (-5.1 – 2.9)	0.592
Waist: hip ratio	0.90 (±0.12)	0.90 (±0.09)	0.00 (-0.05 – 0.04)	0.949	0.139	0.85 (±0.08)	-0.05 (-0.07- - 0.02)	< **0.001***
BM (kg)	74.9 (±17.7)	78.0 (±18.2)	-3.2 (-11.1 – 4.7)	0.425	0.183	71.7 (±11.1)	-3.2 (-7.3 – 2.9)	0.397
Height (cm)	166.0 (±8.2)	164.2 (±8.2)	-1.8 (-5.5. – 1.7)	0.287	0.306	168.1 (±8.6)	2.1 (-1.1 – 5.2)	0.195
BMI (kg/m^2)	27.0 (±5.1)	29.0 (±6.7)	-2.0 (-4.6 – 0.7)	0.143	0.133	25.4 (±3.4)	-1.6 (-3.4 – 0.2)	0.084$^{\#}$
DXA-assessed measures								
ALM (kg)	19.7 (±4.6)	19.9 (±4.6)	-0.1 (-2.2 – 1.9)	0.905	0.148	20.9 (±5.2)	1.2 (0.6 – 2.8)	**0.003***
ALM % (ALM/TBM %)	26.9 (±3.9)	25.5 (±3.9)	1.3 (-0.4 – 3.1)	0.122	0.347	28.8 (±4.2)	1.9 (1.2 – 3.5)	< **0.001***
TLM (kg)	48.2 (±9.4)	49.2 (±10.3)	-1.0 (-5.4 – 3.4)	0.650	0.071$^{\#}$	49.5 (±10.0)	1.3 (-0.2 – 4.6)	0.052$^{\#}$
Total LM % (LM/TBM %)	65.5 (±6.6)	63.3 (±8.0)	2.2 (-1.0 – 5.5)	0.179	0.458	68.6 (±6.8)	3.1 (1.5 – 5.8)	**0.001***
Total FM (kg)	24.2 (±9.2)	27.3 (±11.3)	-3.1 (-7.7 – 1.4)	0.176	0.241	20.4 (±6.2)	-3.8 (-7.1 - -0.8)	**0.014***
BF%	31.5 (±7.0)	33.8 (±8.5)	-2.4 (-5.8 – 1.0)	0.170	0.434	28.3 (±7.2)	-3.2 (-6.1 - -1.5)	**0.001***
Trunk FM (kg)	12.2 (±6.1)	13.9 (±6.4)	-1.6 (-4.4 – 1.1)	0.242	0.252	9.9 (±3.7)	-2.3 (-4.3 - -0.4)	**0.017***

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Data presented as unadjusted mean (±SD). CI = 95 % confidence interval; RA = rheumatoid arthritis; HC = healthy controls; BM = body mass; BMI = body mass index; DXA = dual x-ray absorptiometry; ALM = appendicular lean mass; TLM = total lean mass; FM = fat mass; BF% = % body fat (i.e. FM/BM x 100); unless adjusted by Bonferroni adjustment * = significant ($P < 0.05$); $^{\#}$ = trend ($P = 0.05$ - 0.10); $P^{¥}$ = adjusted significance value when sex included as co-variant due to a difference in the proportion of males to females.

TABLE 6. Objective physical function and self-reported disability for rheumatoid arthritis in 'remission' (DAS28 < 2.6) or not (DAS28 ≥ 2.6)

	'In remission' vs 'Not in remission'					HC vs 'In remission'		
	'In remission' (*n* = 40)	'Not in remission' (*n* = 42)	Absolute difference (CI)	*P*	*P*¥	HC (*n* = 85)	Absolute difference (CI)	*P*¥
IKES (N)	414 (±141)	343 (±130)	71 (10 – 132)	**0.023***	0.052#	477 (±155)	62 (26 - 117)	**0.002***
HGS (kg)	29.6 (±8.3)	22.9 (±9.3)	6.6 (2.7 – 10.5)	**0.001***	**0.002***	33.4 (±10.0)	3.8 (2.4 – 7.4)	**< 0.001***
STS-30 test (reps)	12.3 (±3.3)	11.7 (±3.9)	0.5 (-1.1 – 2.1)	0.513	0.459	16.1 (±4.3)	3.8 (2.3 – 5.3)	**< 0.001***
8'UG (secs)	6.6 (±2.1)	8.2 (±4.9)	-1.6 (-3.3 – 0.1)	0.057#	**0.042***	5.1 (±1.0)	-1.5 (-2.5 - -0.4)	**0.008***
50'W (secs)	9.5 (±2.4)	11.9 (±6.8)	-2.3 (-4.6 - - 0.1)	**0.042***	**0.037***	7.7 (±1.8)	-1.8 (-3.3 - -0.4)	**0.014***

Data presented as unadjusted mean (±SD). CI = 95 % confidence interval; RA = rheumatoid arthritis; HC = healthy controls; IKES = isometric knee extensor strength; HGS = handgrip strength; STS-30 = Sit-to-stands in 30 seconds; 8'UG = 8-foot up and go; 50'W = 50-foot walk; unless adjusted by Bonferroni adjustment * = significant ($P < 0.05$); # = trend ($P = 0.05$ - 0.10); *P*¥ = adjusted significance value when sex included as co-variant due to a difference in the proportion of males to females.