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Original article

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

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Abstract

Objective. RA typically features rheumatoid cachexia [loss of muscle mass (MM) and excessive total fat mass (TFM), 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 aim of this cross-sectional study was to assess the impact of T2T on body composition and objectively assessed function in RA patients.

Methods. A total of 82 RA patients exclusively treated by T2T, were compared with 85 matched sedentary healthy controls (HCs). Body composition was estimated by DXA, with appendicular lean mass the surrogate measure of total MM. Physical function was assessed by knee extensor strength, handgrip strength, 30 s sit-to-stands, 8′ up and go, and 50′ walk (tests which reflect the ability to perform activities of daily living).

Results. Although generally well treated (mean DAS28 = 2.8, with 49% in remission), RA patients had ∼10% proportionally less appendicular lean mass and were considerably fatter (by ∼27%), particularly in the trunk (∼32%), than HCs. 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 with matched HCs was similar to that observed pre-T2T. Additionally, performance of objective function tests was unchanged from that reported by our group for pre-T2T RA patients. Thus T2T, even in responsive RA patients, did not attenuate rheumatoid cachexia or improve objectively assessed function.

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

CLINICAL SCIENCE

Rheumatology key messages

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

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Introduction

RA is characterized 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 (HCs) [2–5] is observed in ~67% of stable RA patients [3, 6–15], while obesity, determined by body composition, is present in ~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 comorbidity 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 (DA), 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 DA, and inflammation in particular [3, 14–15, 27], it would be anticipated that tighter control of DA/inflammation achieved by T2T would better 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 (from ~2008), these studies [4, 6, 8, 10, 18, 20, 29–31] have either exclusively or primarily assessed patients who commenced treatment years prior to the adoption of T2T, and therefore do not inform about 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 HAQ [26, 32, 33]. However, these measures are strongly influenced by pain [34, 35], which diminishes with T2T, and they 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 (HCs). 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]). Finally, 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 Declaration of Helsinki.

Study population

RA patients with stable disease were recruited from outpatient clinics of the Peter Maddison Rheumatology Centre, North Wales. For inclusion, participants had to: fulfil the ACR 2010 revised criteria for RA [37]; be aged $\geqslant$18 years; not be cognitively impaired; be free of other cachectic diseases or conditions preventing safe participation; not be taking anabolic drugs or nutritional supplements; and not be pregnant. Only patients who commenced DMARD treatment following the Peter Maddison Rheumatology Centre's adoption of treatment strategies in-line with the T2T recommendations of Smolen *et al*. [23] (i.e. post 1 January 2008) were included. Once recruited, participants were categorized into either recent-onset ($\leqslant$12 months since diagnosis) or established (>12 months since diagnosis) disease cohorts.

For comparison, sedentary age- and sex-matched HCs were recruited from the local community. To be eligible for the study, HCs 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 MM [3]. The in-house coefficient of variation 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., MA, 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 (ADLs [38]): sit-to-stands in 30 s [STS-30), 8-foot up and go (8′UG) and 50-foot walk (50′W) tests], were also assessed. Performance of each of these strength and function tests, which are routinely used by our group [3, 4, 9–12, 30, 31, 39], was preceded by a submaximal practice.

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Clinical measures

DA was assessed by the DAS28 using CRP, with remission defined as DAS28 < 2.6. Physical disability was subjectively evaluated by the multidimensional HAQ (MDHAQ [40]).

Statistical analysis

The primary outcome was ALM normalized for BM (ALM %), as this is the LM measure most relevant to performing ADLs [i.e. comparing absolute ALM ignores disparities in BM and the effect total fat mass (TFM) has on performing ADLs]. The secondary outcomes included other aspects of body composition [total LM, TFM, trunk FM (trFM) and percentage body fat (BF%)] and the objective physical function measures.

The primary statistical analyses involved comparison of the RA group *vs* the HC group, followed by subanalyses of: recent-onset *vs* established RA patients; RA patients who, at the time of testing, had achieved clinical remission *vs* patients who had not; remission patients *vs* HCs; and finally, informal comparison of current results with our historic, pre-T2T data [3, 4, 9–12, 30, 31; patients for these studies generally commenced treatment 1992–2004]. Statistical analysis involved multiple or univariate analysis of variance according to appropriateness, and chi-squared tests were used for comparison of dichotomous variables. Significance was set at $P < 0.05$, and a trend was recognized as $P = 0.05$–0.10. Data is presented as mean (S.D.).

Results

A total of 197 (n = 197) patients with RA were deemed eligible for the study and approached. Of these, 115 (58%) declined participation (primarily due to: not being 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), while the remaining 49 had a disease duration of 1–7 years (established group; mean duration ∼2 years 11 months). A total of 85 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 HCs. 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 summarized 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: $P = 0.625$–0.905).

Anthropometry and body composition

Anthropometric and DXA-assessed body composition data appear in Table 2. Despite being shorter (by mean ∼3 cm, $P = 0.019$), RA patients were heavier (mean BM: +4.8 kg, $P = 0.093$), and consequently their mean BMI was higher ($P = 0.002$) than that of HCs. RA patients also had a greater mean waist circumference (+7.7 cm, $P = 0.001$) and waist:hip ratio ($P < 0.001$) than HCs.

When adjusted for BM (i.e. percentage of), RA patients had ∼10% less muscle than HCs (ALM %, $P < 0.001$). This relative deficit corresponds with the proportional loss of ALM we observed in stable RA patients, of similar age and gender distribution, who had commenced treatment ∼1992–2004 (i.e. ∼9%, RA n = 23, matched HCs, n = 23 [4]; ∼11%, RA n = 20, matched HCs, n = 20 [3]). When expressed absolutely (kg), RA patients in the current study exhibited less ALM (−1.1 kg) and total lean mass (−0.8 kg) than the HCs, although these differences were not statistically significant.

DXA-assessed body composition confirmed that RA patients were considerably fatter than HCs, with the group differences in BM more than accounted for by higher TFM in patients (+5.4 kg, 26.5% greater, $P < 0.001$). Consequently, BF% was also higher in patients ($P < 0.001$). As anticipated, the majority of this increased adiposity was situated on the trunk (+3.2 kg, 32.3% higher than HCs, $P = 0.001$). In pre-T2T patients we had noted mean increases in TFM of ∼17% [4] and ∼13% [3] relative to HCs. No differences in anthropometric or DXA measures were evident between the recent-onset and established, or between seropositive and seronegative RA patients (data not shown; $P = 0.581$–0.998).

Objective physical function

Compared with HCs, RA patients performed poorly in each of the objective function measures (Table 3): IKES was 24.3% less ($P < 0.001$); HGS, 25.3% less ($P < 0.001$); STS-30, 34.2% less ($P < 0.001$); 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 s, overall mean = 6.2 (*vs* 7.4 s) [4, 30, 31]; 50′W mean range 9.1–10.0 s, overall mean = 9.5 (*vs* 10.7 s) [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-

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TABLE 1 Demographic and clinical characteristics for RA patients and sedentary, age- and sex-matched HCs

Characteristic	RA (n = 82)	HC (n = 85)	P-value
Age, mean (S.D.), years	60.9 (11.7)	60.9 (8.1)	0.962
Sex, female, n (%)	53 (65)	55 (65)	0.992
Disease duration, mean (S.D.), months	23.8 (19.0)	–	–
Seropositive RA, n (%)	67 (85)	–	–
DAS28 (0–10), mean (S.D.)	2.8 (1.0)	–	–
Medications, n (%)			
MTX[a]	68 (83)	–	–
HCQ	26 (32)	–	–
LEF	7 (9)	–	–
SSZ	5 (6)	–	–
Tacrolimus	3 (4)	–	–
MMF	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	18 (22)	3 (5)	<0.001*
Ex-smokers	39 (48)	25 (31)	<0.016*
Never smokers	25 (30)	52 (61)	<0.001*
Subjective measure of disability			
MDHAQ score (0–3), mean (S.D.)	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*

Differences at baseline were assessed using analyses of variance or chi-square test as appropriate. [a]Supplemented with folate. [b]Double or triple DMARD therapy. [c]Current corticosteroid range 5.0–10.0 mg/day. [d]Corticosteroid inhaler for asthma. [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. * < 0.05. MDHAQ: multi-dimensional health assessment questionnaire; HC: healthy control group; Seropositive RA: RF and/or anti-CCP seropositive.

TABLE 2 Body composition measures for RA patients and sedentary, age- and sex-matched HCs

Variable	RA (n = 82)	HC (n = 85)	% difference (CI for absolute difference)	P-value
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), height (cm)	76.5 (17.9) 165.1 (7.9)	71.7 (11.1) 168.1 (8.6)	↑ 6.3 (0.2, 9.3) ↓ 3.0 (0.5, 5.5)	0.093[†] 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*
TFM (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*
TrFM (kg)	13.1 (6.3)	9.9 (3.7)	↑ 32.3 (1.6, 4.8)	0.001*

Data presented as mean (S.D.). Unless adjusted by Bonferroni adjustment. *P < 0.05, [†]trend (P = 0.05–0.10). HC: healthy control group; BM: body mass; ALM: appendicular lean mass; TLM: total lean mass; TFM: total fat mass; TrFM: trunk fat mass; BF%: % body fat (i.e. FM/BM × 100); ↑: higher in RA patients relative to matched HCs, ↓: lower in RA patients relative to matched HCs.

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TABLE 3 Objective physical function and self-reported disability for RA patients and sedentary, age- and sex-matched HCs

Variable	RA (n = 82)	HC (n = 85)	Absolute difference (% difference) (CI)	P-value
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 (s)	7.4 (3.9)	5.1 (1.0)	↑ 2.3 (31.1) (1.4, 3.1)	<0.001*
50′W (s)	10.7 (5.3)	7.7 (1.8)	↑ 3.0 (28.0) (1.8, 4.3)	<0.001*

Data presented as mean (S.D.). Unless adjusted by Bonferroni adjustment. *$P < 0.05$. HC: healthy control group; IKES: isometric knee extensor strength; HGS: handgrip strength; STS-30: Sit-to-stands in 30 s; 8′UG: 8-foot up and go; 50′W: 50-foot walk; ↑: higher in RA patients relative to matched-HCs, ↓: lower in RA patients relative to matched-HCs.

onset and established RA patients (data not shown; P = 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 HCs, 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 *vs* 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 with 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; TFM, P = 0.014; BF%, P = 0.001; TrFM, 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 HCs.

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 showed that our T2T RA patients, including those who had achieved clinical remission, continued to have substantially reduced MM, 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 of our patients, both of which indicate that our cohort was well-treated and generally benefiting from the T2T approach.

While the precise mechanisms underlying rheumatoid cachexia remain unclear, DA (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 MM of ~10% observed in our current patients relative to matched, sedentary HCs was similar to what we had noted in stable, pre-T2T RA patients {~9%, for patients with a mean RA DA 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; that is, 12% [5], 8% [42], 9% [43] (data collection 2004–06), 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 2004–05) found an 11% reduction in DXA-assessed fat-free mass index/height $(m)^2$ of RA patients with active disease (mean DAS28 = 5.5) *vs* a matched European reference population.

The elevated adiposity we observed in our T2T RA patients relative to sedentary controls [TFM (kg) increased by 26.5%, BF% increased 15.5%, TrFM increased 32.3%] is also consistent with the observations made in our pre-T2T RA patients (TFM increases of ~17% [4] and ~13% [3] *vs* HCs), and generally with the DXA-assessed disparities in adiposity reported by others in stable, pre-T2T RA patients relative to matched HCs [TFM (kg) increased by 12% [5]; TFM and TrFM increased 13% and 25%, respectively [43]; TFM and trunk TrFM increased 12.5% and 13.5% in females, and 5.4% and 7.1% in males, respectively [42]; TFM and TrFM increased 13.5% and

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TABLE 4 Demographic and clinical characteristics for RA patients in remission *vs* those not in remission[a]

Characteristic	In remission *vs* not in remission			HC *vs* In remission	
	In remission (n = 40)	Not in remission (n = 42)	P-value	HC (n = 85)	P-value
Age, mean (S.D.), years	60.4 (12.2)	61.4 (11.3)	0.706	60.9 (8.1)	0.764
Sex, female, n (%)	23 (58)	30 (71)	0.187	55 (65)	0.435
Disease duration, mean (S.D.), months	23.1 (17.5)	24.5 (20.6)	0.740	–	–
Seropositive RA, n (%)	32 (80)	35 (83)	0.886	–	–
DAS28 (0–10), mean (S.D.)	2.0 (0.4)	3.6 (0.8)	<0.001*	–	–
CRP (mg/l), mean (S.D.)	7.3 (7.7)	13.1 (14.4)	0.024*	–	–
Medications, n (%)					
MTX[a]	34 (85)	34 (81)	0.626	–	–
HCQ	3 (8)	2 (5)	0.604	–	–
LEF	3 (8)	4 (10)	0.743	–	–
SSZ	13 (33)	13 (31)	0.880	–	–
Tacrolimus	1 (3)	1 (2)	0.972	–	–
MMF	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 DMARDs	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	7 (18)	11 (26)	0.180	3 (5)	0.014*
Ex-smokers	19 (48)	20 (48)	0.493	25 (31)	0.007*
Never smokers	14 (35)	11 (26)	0.542	52 (61)	0.001*
Subjective measure of disability					
MDHAQ score (0–3), mean (S.D.)	0.32 (±0.32)	0.81 (±0.59)	<0.001*	0.08 (±0.04)	0.001*
Exercise frequency, n (%)[e]					
Exercise frequency score (0–3), mean (S.D.)	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*

Differences at baseline were assessed using analyses of variance or Chi-square test as appropriate. [a]Patients in remission have DAS28 < 2.6; those not in remission have DAS28 ⩾ 2.6. [b]Supplemented with folate. [c]Double or triple DMARD therapy. [d]Current corticosteroid range 5.0–10.0 mg/day. [e]Corticosteroid inhaler for asthma. [f]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. *P < 0.05; Seropositive RA: RF and/or anti-CCP seropositive; MDHAQ: multi-dimensional health assessment questionnaire.

21.6%, respectively, in females, with no additional adiposity in males [2]; and TFM and TrFM increased 15.3% and 19.4%, respectively, in females, with no additional adiposity in males [44]. While the RA patients in the current study were more sedentary than the HCs, the between-group difference only amounted to ~30 min walking/week, and both groups fall well short of the minimum recommendation for long-term loss of TFM of 250 min/week of moderate intensity physical activity [45]. This 30 min disparity in low–moderate intensity physical activity would also not account for the difference in muscle mass, as higher-intensity exercise is required for eliciting hypertrophy [45]. Thus, our findings clearly indicate that rheumatoid cachexia had not been resolved, or even attenuated, by tight control of DA, despite the other clinical benefits this approach conferred.

We also demonstrated in this study that objectively assessed physical function did not improve with T2T therapy. This finding is not surprising in view of the lack of improvement in either muscle or TFMs, and the strong association between these and physical function in RA patients [16, 20–22]. In our T2T patients, strength relative to HCs was reduced by ~25%, and the performance level on tests designed to reflect the ability to perform ADLs and live independently [38] was reduced by about a third. More tellingly with regard to the effect of T2T on function, the test scores obtained by patients in the current study were not better, and in some cases were worse (8′UG,

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Table 5 Body composition measures for RA patients in remission *vs* those not in remission[a]

Variable	In remission *vs* not in remission					HC *vs* in remission		
	In remission (n = 40)	Not in remission (n = 42)	Absolute difference (CI)	P-value	P-value[b]	HC (n = 85)	Absolute difference (CI)	P-value
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) Height (cm)	74.9 (17.7) 166.0 (8.2)	78.0 (18.2) 164.2 (8.2)	−3.2 (−11.1, 4.7) −1.8 (−5.5, 1.7)	0.425 0.287	0.183 0.306	71.7 (11.1) 168.1 (8.6)	−3.2 (−7.3, 2.9) 2.1 (−1.1, 5.2)	0.397 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*
TFM (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*
TrFM (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*

Data presented as unadjusted mean (S.D.). [a]Patients in remission have DAS28 < 2.6; those not in remission have DAS28 ⩾ 2.6. [b]Adjusted significance value when sex included as covariant due to a difference in the proportion of males to females. HC: healthy controls; BM: body mass; ALM: appendicular lean mass; TLM: total lean mass; TFM: total fat mass; TrFM: trunk fat mass; BF%: % body fat (i.e. FM/BM × 100); unless adjusted by Bonferroni adjustment *P < 0.05. [†]Trend (P = 0.05–0.10).

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Table 6 Objective physical function and self-reported disability for RA patients in remission *vs* those not in remission[a]

Variable	In remission *vs* Not in remission					HC *vs* In remission		
	In remission (n = 40)	Not in remission (n = 42)	Absolute difference (CI)	P-value	P-value[b]	HC (n = 85)	Absolute difference (CI)	P-value
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 (s)	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 (s)	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 (S.D.). [a]Patients in remission have DAS28 < 2.6; those not in remission have DAS28 ⩾ 2.6. [b]Adjusted significance value when sex included as co-variant due to a difference in the proportion of males to females. Unless adjusted by Bonferroni adjustment. *P < 0.05. †Trend (P = 0.05–0.10). HC: healthy controls; IKES: isometric knee extensor strength; HGS: handgrip strength; STS-30: Sit-to-stands in 30 s; 8′UG: 8-foot up and go; 50′W: 50-foot walk.

50′W), than those of patients in our earlier studies [3, 4, 9–12, 30, 31] who were of similar age and gender distribution. To provide a context for how poor the physical function of our T2T RA patients was, we referred to the study of Rikli and Jones [38], who recently published minimal fitness standards compatible with living independently late in life using objective tests (including STS-30 and 8′UG). In the present study, the RA women (mean age 58.6 years) achieved a STS-30 score appropriate for healthy moderate functioning women aged 80–84 years, and the RA men (mean age of 65.0 years) a score in line with healthy moderate functioning men of 85–89 years. For the 8′UG test, the respective equivalents were 85–89 years for the women, and the men failed to achieve the standard of 90–94-year-old healthy men (the highest age category). Hence, on average, both the female and male patients had the function of healthy individuals ∼25 years older.

Despite the substantial deficits in objectively measured physical function (28–34% worse than sedentary HCs), it is revealing that the patients generally rated their disability as only being mild (mean MDHAQ = 0.57). Also of interest, is that our earlier (pre-T2T) patients, although generally performing the objective tests as well, if not better than, the recent T2T patients, subjectively rated their disability as being higher (e.g. data collected 2005–07, baseline means; DAS28 = 3.3, STS30 = 12.5 reps, 50′W = 9.3 s, IKES = 323 N, MDHAQ = 0.91 [9]). This improvement in subjectively assessed function (e.g. HAQ, MDHAQ) with T2T has been widely reported [26, 32, 33] and may be due to reductions in pain [25], as pain is known to strongly influence HAQ scores [34, 35, 46]. This discord between objectively and subjectively assessed function in stable RA patients, 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 normalization 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 one-fifth to one-third poorer than sedentary HCs]. Additionally, we may have underestimated the extent of functional loss (and the perturbations in body composition) existing in broader RA populations, because 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 had 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 among 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 preclinical stage), and thus prior to the initiation of treatment. This proposal is consistent with: the absence of differences in anthropometric, body composition or physical function measures between our recent and established RA patients; reports of a similar incidence and magnitude of rheumatoid cachexia in recently diagnosed RA patients as for established patients [2, 12]; indications that the rate of muscle loss in established, controlled patients is similar to that of healthy individuals [10, 44]; and the consistent findings that disease processes, including inflammation and co-morbidity risk, are already elevated in the preclinical period [48].

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To summarize, 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 because the T2T regimen posits that the 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.

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