Body composition in patients with rheumatoid arthritis: a narrative literature review

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Abstract

There is growing interest in the alterations in body composition (BC) that accompany rheumatoid arthritis (RA). The purpose of this review is to (i) investigate how BC is currently measured in RA patients, (ii) describe alterations in body composition in RA patients and (iii) evaluate the effect on nutrition, physical training, and treatments; that is, corticosteroids and biologic Disease Modifying Anti-Rheumatic Disease (bDMARDs), on BC in RA patients.

The primary-source literature for this review was acquired using PubMed, Scopus and Cochrane database searches for articles published up to March 2021. The Medical Subject Headings (MeSH) terms used were 'Arthritis, Rheumatoid', 'body composition', 'sarcopenia', 'obesity', 'cachexia', 'Absorptiometry, Photon' and 'Electric Impedance'. The titles and abstracts of all articles were reviewed for relevant subjects.

Whole-BC measurements were usually performed using dual energy x-ray absorptiometry (DXA) to quantify lean- and fat-mass parameters. In RA patients, lean mass is lower and adiposity is higher than in healthy controls, both in men and women. The prevalence of abnormal BC conditions such as overfat, sarcopenia and sarcopenic obesity is significantly higher in RA patients than in healthy controls; these alterations in BC are observed even at an early stage of the disease. Data on the effect treatments on BC in RA patients are scarce. In the few studies published, (a) creatine supplementation and progressive resistance training induce a slight and temporary increase in lean mass, (b) exposure to corticosteroids induces a gain in fat mass and (c) tumour necrosis factor alpha (TNFα) inhibitors might be associated with a gain in fat mass, while tocilizumab might be associated with a gain in lean mass.

The available data clearly demonstrate that alterations in BC occur in RA patients, but data on the effect of treatments, especially bDMARDs, are inconsistent and further studies are needed in this area.

Keywords: body composition, body fat and lean mass, dual energy x-ray absorptiometry, rheumatoid arthritis

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Background

Rheumatoid arthritis (RA) is a systemic, immune-mediated disease, characterised by synovitis and/or inflammation of periarticular structures and systemic inflammation.[1] RA is the most prevalent inflammatory rheumatic disease, with estimated prevalence rates in European adults ranging from 3.1 to 8.5 cases per 10,000.[2] Patients with RA exhibit alterations in quality of life and a high prevalence of fatigue and depression.[3,4] The disease also constitutes a major global health burden, as measured in disability-adjusted life years (DALYs).[5]

Twenty years ago, RA often led to joint destruction and considerable disability. Since then, scientific progress has prompted major advances in the treatment of the disease. Disease Modifying Anti-Rheumatic Drugs (DMARDs), such as conventional synthetic DMARDs (csDMARDs, e.g. methotrexate), biologic DMARDs [bDMARDs, e.g. tumour necrosis factor alpha (TNFα) inhibitors] and targeting synthetic DMARDs [tsDMARDs, e.g. janus kinase (JAK) inhibitors], can control disease activity and thus prevent joint destruction.[6–9] Moreover, in the last 20 years, RA has become milder, with patients exhibiting fewer severe extra-articular manifestations and lower mortality rates.[10,11] However, patients with RA still exhibit excess mortality, especially from cardiovascular disease.[12] As such, for RA patients, better evaluation of comorbidities and patients' cardio-metabolic profiles is essential.[13,14]

In addition to joint damage and comorbidities, alterations in body composition have been observed in patients with RA.[15,16] Systemic inflammation is the main factor underlying these alterations, but several other factors, such as malnutrition, physical disability, comorbidities, corticosteroids and bDMARDs, may also induce alterations in body composition in RA patients.[17,18] Evidence suggests that the proportions and distribution of fat and lean mass throughout the body have important implications for health. Low lean mass and excess body fat are predictors of poor health outcomes in the general population.[19] Low lean mass at its most extreme (a condition known as cachexia) may lead to weakness, disability and metabolic abnormalities.[20–22] Gains in fat mass may predispose to obesity, diabetes, hypertension and risk of cardiovascular disease.[12,23–25] A better understanding of the alterations in body composition that occur in RA patients (including those receiving bDMARDs) is important because of the many potential implications in terms of outcome, such as disability and cardio-metabolic risk.

The purpose of this review is three-fold: (i) to investigate how body composition is currently measured in RA patients, and which parameters are associated with abnormal body composition conditions in those patients, (ii) to investigate alterations in body composition in RA patients compared with healthy controls and (iii) to investigate the effect of nutrition, physical training and treatments (corticosteroids and bDMARDs) on body composition in RA patients.

Methods

Data sources
For this manuscript, the authors searched the PubMed, Scopus and Cochrane databases for articles published up to March 2021. We also searched for conference abstracts from selected Rheumatology meetings: European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR); and from Nutrition meetings: International Congress of Nutrition, European Nutrition Conference and American Society of Nutrition, from 2018 to 2020. We manually reviewed them for inclusion.

Search terms
The Medical Subject Headings (MeSH) terms used were 'Arthritis, Rheumatoid', 'body composition', 'sarcopenia', 'obesity', 'cachexia', 'Absorptiometry, Photon' and 'Electric Impedance', in the following combination: ['Arthritis, Rheumatoid' (Mesh)] AND ['Body Composition' (Mesh) OR 'Electric Impedance' (Mesh) OR 'Obesity' (Mesh) OR 'Cachexia' (Mesh) OR 'Sarcopenia' (Mesh)].

Inclusion/exclusion criteria
Searches were restricted to adults ≥18 years old and human studies in the English language. All types of original studies, including clinical trials, cohort studies, case-control studies, conference abstracts and cross-sectional studies, as well as meta-analyses and reviews were included and analysed. As the definition of sarcopenia has changed with time, we included studies in which sarcopenia is fully described and publications in which patients are reported as having sarcopenia defined as low muscle mass. Protocols, case reports and studies which did not assess whole-body composition were excluded. The terms 'bone assessment' and 'osteoporosis' were excluded from our search. Indeed, bone fragility in patients with RA is beyond the scope of this paper and a detailed discussion of this topic can be found in excellent reviews elsewhere.[26–28]

The results of the bibliographic search are shown in Supplemental Figure 1.

Measurement of body composition in RA patients

Definition of body composition

The term 'body composition' does not refer to an anatomic view of the body, with a description of each tissue and its localization. Instead, it refers to a description of the body from a chemical point of view. For example, the three-compartment model includes two major components (fat mass and fat-free mass) and a minor component (mineral content).[29] Body composition is not stable. It is dynamic and variable, with changes occurring in response to external or internal stimuli.[30] Body composition is a 'living memory' of what we have eaten or experienced. Experiences that affect body composition include trauma, infections and chronic systemic inflammation.[31] The assessment of body composition provides insights into both the nutritional status and functional capacity of the human body.[32] Several techniques are used to measure it. In this review, we focus on those techniques that are used to assess whole-body composition, such as dual energy x-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA). Body parts assessment of body composition using computed tomography (CT), (high resolution) peripheral quantitative CT, bedside ultrasound (US), or magnetic resonance imaging (MRI) is beyond the scope of this review.

Currently available techniques (Supplemental Table 1)

Dual energy x-ray absorptiometry. Dual energy x-ray absorptiometry (DXA) was primarily used to assess bone mineral density (BMD) and to diagnose osteoporosis.[33] DXA measures energy absorption at two X-ray photon energy levels. By measuring the intensities of the absorbed energy in this way, it is possible to differentiate between bone, fat mass and fat-free mass (FFM), which is also known as 'soft tissue lean mass' (i.e. non-bone and non-fat soft tissue), as since these tissues have different X-ray attenuation profiles.[34] Nowadays, DXA is recognized as the gold standard for assessing body composition.[35] It provides a means of quantifying fat and lean masses, both in a single body region (e.g. arms and legs) and at the whole-body level. With the latest generation of densitometers, body composition can be assessed with a single whole-body scan, with low exposure to radiation [1 μSv, less than a standard X-ray (100 μSv)] and fast acquisition times.[34] Other benefits of this technology include simplicity,

moderate cost, availability and accuracy. DXA is also used to assess BMD and visceral adipose tissue (VAT). VAT is associated with metabolic syndrome and cardiovascular risk.[36–39] However, there are limitations to using DXA to assess body composition: trunk muscles, for instance, are difficult to evaluate using DXA. Therefore, if DXA fat mass and lean mass measurements are derived from arms and legs, they might over- or underestimate the extent of low muscle mass and obesity.[40] In addition, oedema or dehydration can bias DXA muscle and fat measurements.[41]

Bioelectrical impedance analysis. BIA is used to assess body composition by passing a low intensity (500–800 mA), high frequency (50 kHz) current through the body and then measuring several electrical parameters (resistance, reactance, impedance and phase angle). The measurements obtained provide indirect estimates of whole-body composition. BIA assesses total body water and can predict the amount of FFM. Its use is based on several assumptions, namely that (1) the human body is divided into five cylinders, that is, the trunk and the upper and lower extremities, with uniform electric conductivity; (2) FFM contains virtually all of the water and conduction electrolytes in the body; (3) FFM hydration is constant and (4) conductive length equates to stature.[42] BIA can be used to assess body composition in elderly and obese patients, as well as in patients with cancer or infections.[42–44] The benefits of BIA include ease of use, affordability, portability of the device, absence of radiation exposure and non-invasiveness of the technique. It appears to correlate well with DXA and CT.[38,45] The limitations of BIA as a means of assessing body composition include the fact that (1) it is an indirect method, (2) it cannot be used to assess BMD and VAT and (3) every specific population assessment requires its own equation.[45]

Parameters measured by DXA

Of all the techniques used to assess body composition, DXA seems to be the best compromise between accuracy and accessibility. As DXA is the technique used in most of the studies included in this review, it is important to explain the main parameters of this technique.

In 2019, the International Society for Clinical Densitometry (ISCD) published an updated official position on whole-body composition assessment with DXA.[46] According to the ISCD, where

adults are concerned, total body (with head) values of body mass index (BMI), total body mass (TBM), total lean mass (TLM), total fat mass (FM) and percent body fat (PBF) should appear on all reports (Supplemental Table 2). Moreover, optional DXA measurements of adiposity and lean mass include VAT (cm²), fat mass index (FMI: FM/height²), appendicular lean mass (ALM, kg), appendicular lean mass index (ALMI: ALM/height²) and skeletal muscle index (SMI: TLM/height²). Data are also lacking on changes in VAT. Indeed, using DXA to measure VAT is a recent practice, but not all DXA machines are designed to do so. Fat-free mass and fat-free mass index (FFMI: FFM/height²) are sometimes reported. The clinical utility of these latter measurements (FFM and FFMI) is currently uncertain. As such, only the recommended DXA parameters and optional DXA parameters, if available, are reported from the studies included in this review.

Categories of abnormal body composition conditions

Overfat. The term 'obesity' is commonly used to refer to a BMI $\geqslant 30$ kg/m². However, in RA studies, the term 'overfat' is used to refer to excess adiposity (PBF). For instance, in the criteria proposed by Cesari *et al.*,[47] people aged 60–79 years-old were defined as 'overfat' if their PBF was >31% in white men, >29% in African American men, >29% in Asian men, >43% in white women, >41% in African American women and >41% in Asian women.

Sarcopenia. Sarcopenia is a condition that is commonly associated with ageing. It is characterised by the loss of muscle mass and muscle strength, leading to impaired muscle function. However, in RA studies on body composition, 'sarcopenia' is generally used to refer to low lean mass (ALM, ALMI or SMI) alone using various cut-offs (Supplemental Table 3).[19,35,48–55] For instance, in the criteria proposed by Baumgartner *et al.*,[48] the mean ALMIs of young male and female reference groups, minus two standard deviations (SDs), were defined as the gender-specific cut-offs for sarcopenia, that is, 7.26 kg/m² for men and 5.5 kg/m² for women.

A quantitative assessment is not enough to establish a diagnosis of sarcopenia. A comprehensive assessment of muscle, muscle strength and muscle function are also required. Sarcopenia is characterised by a loss of lean mass leading to impaired muscle function.[56] It could also lead to physical disability, falls, fractures and even cardiovascular diseases.[57,58] While many definitions of sarcopenia have been proposed, the most commonly accepted definition is the one published in 2010 by the European Working Group on Sarcopenia in Older People (EWGSOP).[35] In 2019, the EWGSOP published an update to the definition (Supplemental Figure 2). Sarcopenia is now considered a muscle disease (muscle failure), with low muscle strength superseding low muscle mass as a principal determinant. If there is a suspicion of sarcopenia, muscle strength must be assessed.[19] Sarcopenia is probable if low muscle strength is established (i.e. grip strength <26 kg for men and <16 kg for women OR chair stand >15s for five rises). The diagnosis is confirmed if low muscle mass (i.e. ALM/height² <7.0 kg/m² for men and <5.5 kg/m² for women, OR ALM <20 kg for men and <15 kg for women:) or quality (i.e. gait speed $\leqslant 0.8$ m/s, Short Physical Performance Battery $\leqslant 8$ point score, Timed-up-and-go test $\geqslant 20$s or non-completion or $\geqslant 6$ min for completion of 400 m walk test) is also established. When low muscle strength, low muscle mass/quality and low physical performance are all established, sarcopenia is considered severe.[19]

Sarcopenic obesity. In RA studies on whole-body composition, the term 'sarcopenic obesity' is used to refer to a loss of lean mass concurrent with excess adiposity (PBF). For instance, according to Giles *et al.*,[16] sarcopenic obesity was defined as fulfilling the criteria for both sarcopenia (as proposed by Janssen *et al.*[49]) and overfat (as proposed by Cesari *et al.*[47]).

Rheumatoid cachexia. The term 'classic cachexia' is used to refer to the condition that is characterised by severe loss of weight, fat and muscle mass, accompanied by an increase in protein catabolism due to underlying disease(s).[59]

Despite numerous publications on 'rheumatoid cachexia' (RC), there is no consensus on the clinical criteria for its diagnosis. RC is a dramatic change in body composition characterised by the loss of muscle mass with or without loss of fat mass, resulting in no or limited changes in BMI.[60]

The most used criteria for establishing RC are those proposed by Engvall *et al.*,[61] that is FFMI below the 10th percentile and FMI above the 25th percentile. Data from a Swiss population

sample of healthy adults (2986 men and 2649 women) were used to establish a body composition index that determines RC.

Sarcopenia and rheumatoid cachexia: two different conditions!. As the loss of muscle mass is commonly evaluated in both RC and sarcopenia, these syndromes are often confused with one another. However, the diagnosis of sarcopenia is established based on an assessment of muscle alone, while the diagnosis of RC is based on an assessment of both muscle and fat.

Alterations in body composition in rheumatoid arthritis

Body composition in RA patients was assessed (mainly by DXA) in several studies. We drew a distinction between studies that included patients with early RA and those that included patients with established RA. Moreover, data on the prevalence of abnormal body composition conditions (sarcopenia, overfat, sarcopenic obesity and RC) are also reported, if available. Results are summarized in Table 1.

Early rheumatoid arthritis

We found four case-control studies ($n = 105$–317 cases) in which alterations in body composition were assessed in patients with early RA.[15,62–65]

In 2009, Book *et al.*[15] compared with 132 early RA patients (women: 72%; mean age: ~60 years old; disease duration: ≤1 year) with controls matched one-to-one for age and sex. All of the patients who had been treated with corticosteroids or csD-MARDs prior to inclusion had been treated for fewer than 30 days. Fewer women (31%) than men (38%) had been treated with corticosteroids, with a mean daily dose of 6.5 and 8.0 mg, respectively. Body composition was assessed by DXA. Appendicular lean mass was lower in RA patients compared with controls in both women and men (women: 16.8 *versus* 17.6 kg, $p = 0.007$; men: 23.0 *versus* 25.8 kg, $p < 0.001$). TLM was significantly lower in RA men (but not RA women) (54.4 *versus* 58.3 kg, $p = 0.012$), whereas weight, BMI and FM were significantly higher in RA women (but not RA men) (68.1 *versus* 64.0 kg, $p = 0.016$; 25.1 *versus* 23.7 kg/m², $p = 0.012$; and 26.1 *versus* 23.0 kg, $p = 0.014$, respectively).

In a longitudinal follow-up of their previous study, Book *et al.*[62] compared 63 RA patients

(women: 71%; mean age of women: 58.3 years; mean age of men: 60.7 years; mean disease duration: 7 months) with 63 healthy controls matched for age and sex. At 2 years, the changes observed in the RA group were generally less pronounced than those observed in the control group. In both men and women, loss of TLM was significantly less in RA patients compared with controls (women: −0.29 *versus* −1.48 kg, $p = 0.002$; men: 0.09 *versus* −2.94 kg, $p = 0.002$) and gain in FM was significantly less in female patients compared with female controls (0.44 *versus* 2.83 kg, $p = 0.002$).[62] However, due to the small sample size and the modest follow-up time, no definitive conclusions can be drawn and this study was conducted in the pre-bDMARDs era.

The occurrence of alterations in body composition in early RA was confirmed in three studies.[63–65] In 105 Vietnamese women with RA (disease duration ≤3 years) compared with healthy age-matched controls, mean weight and BMI values were similar, but higher FM (19.1 *versus* 16.9 kg, $p = 0.007$) and lower ALM (12.9 *versus* 14.1 kg, $p = 0.02$) were observed.[63] Moreover, the prevalence of abnormal body composition conditions was significantly higher in RA patients compared with controls (all $p < 0.001$): (i) sarcopenia (18.1 *versus* 9.5%, using the criteria proposed by Hull *et al.*[84]), (ii) overfat (41.9 *versus* 31.4%, using the criteria proposed by Gallagher *et al.*[85]) and **(iii)** sarcopenic obesity (12.4 *versus* 3.8%, using the criteria for both sarcopenia and overfat).[63] In another recent study, the cohort was composed of 317 early arthritis patients (symptom duration ≤2 years; 84% RA according to 2010 ACR/EULAR criteria[86]) with no prior treatment with DMARDs.[64] Mean age was 61 ± 7 years and mean BMI was 28.0 kg/m². The cohort was compared with 1268 non-arthritis controls from the Rotterdam study, matched one-to-four for age, gender and ethnicity (Caucasian, African or Asian).[87] Compared with controls, BMI and FMI were higher (both $p < 0.01$) in arthritic women (but not in men), ALMI was lower in both sexes ($p < 0.01$) and sarcopenia was 4–5 times more common in early arthritis patients than in controls (women: 5.5 *versus* 1.3%; men: 8.2 *versus* 1.5%; both $p < 0.01$; using the criteria proposed by Baumgartner *et al.*[48]). Similar results (higher PBF and lower ALM in RA patients) were found in an Estonian study.[65] In that study, the authors compared the DXA-acquired body composition data of 91 early RA patients (72% women) with those of 328 controls (54%) women. 41.8% of

Table 1. Body composition in patients with early and established RA *versus* controls.

References	Patients (*n*)	Controls	Mean age in years	Disease duration	Conclusion
Book *et al.*[15]	132 (95F/37M)	132 (95F/37M) matched for current smoking when possible.	58.4 ± 15.8 (F)	7.5 ± 2.8 months (F)	Lower ALM, higher BMI, higher FM and higher trunk fat mass in Female RA patients
			64.5 ± 9.7 (M)	7.3 ± 2.7 months (M)	Lower TLM and lower ALM in Male RA patients
Book *et al.*[62]	63 patients (45F/18M) 63 controls matched for sex and age	Early treatment with DMARDs	58.3 ± 15.7 in F patients 66.2 ± 11.5 in M patients	7.2 ± 2.9 in F patients	In both men and women TLM decreased significantly less in patients compared with controls, *p* = 0.002 for women and *p* = 0.002 for men
				7.6 ± 3.0 in M patients	FM increased significantly less in female patients compared with female controls (*p* = 0.002)
Dao *et al.*[63]	105 F	105 matched for age	56.3 ± 8.7	21.6 ± 2.8 months	Higher BMI, FM and PBF in RA patients Higher prevalence of sarcopenia, overfat and sarcopenic obesity in Female RA patients.
Turk *et al.*[64]	317 (219F/98M)	1268 (875F/393M) from the Rotterdam Study II[3] and matched for ethnicity, gender and age	61.0 ± 7.0	7 (3–22) months	Lower ALMI (both in F and M), higher BMI and FMI (F)
					Sarcopenia 4–5 times more common in RA patients than in controls
Müller *et al.*[65]	91 (66F/25M)	328 matched for sex and age	52 ± 2	215 ± 24 days	Higher PBF and lower in RA patients
Giles *et al.*[16]	189 (117F/72M)	189 matched for sex, race and age	59.9 ± 8.4	9 (5–17) years	Higher BMI, higher FM, higher FMI, higher trunk fat mass, higher PBF and lower TLM/FM in Female RA patients
					Higher prevalence of sarcopenia, overfat and sarcopenic obesity in Female RA patients.
					Lower ALM in Male RA patients
Reina *et al.*[66]	89F	100 matched for age	62 ± 8	13.7 ± 9.5 years	ALM, ALMI and TLM lower in RA patients
					Higher prevalence of sarcopenia in RA patients than in controls
Elkan *et al.*[67]	60 (50F/10M)	Age- and sex-matched European reference population	F: 65.5 (60.0–75.0) M: 60.5 (55.0–67.0)	F: 13.0 (9.0–23.0) years M: 15.5 (6.0–24.0) years	Higher BMI and lower FFM/FFMI in F RA patients. Higher FM and FMI in RA patients compared with reference population
Lemmey *et al.*[68]	82 (53F/29M)	85 matched for sex and age	60.9 ± 11.7	23.8 ± 19.0 months	Higher PBF and FM and lower % ALM in RA patients
Delgado-Frías *et al.*[69]	100F	98 matched for age	55.6 ± 9.3	NR	No difference between the two groups

(continued)

Table 1. (continued)

References	Patients (*n*)	Controls	Mean age in years	Disease duration	Conclusion
Ngeuleu *et al.*[70]	123 (107F/16M)	No controls	52.3 ± 13.2	9.8 ± 8 years	40% of patients diagnosed with sarcopenia
Vliestra *et al.*[71]	82 (60F/15M)	75 patients with osteoarthritis (45F/30M)	61.1 (13.3)	NR	17.1% of RA patients diagnosed with sarcopenia *versus* 29.3% of patients with osteoarthritis (non-significant)
					Higher prevalence of sarcopenic obesity in patients with osteoarthritis
Torii *et al.*[72]	388F	No controls	65 (54.3–72.0)	9 (4.0–21.0) years	37.1% of patients classified as having sarcopenia (14.7%: severe sarcopenia, 22.4%: sarcopenia)
Lin *et al.*[73]	457 (378F/79M)	1860 non matched	49.5 ± 13.1	54 (24–118) months	Lower ALMI in RA patients
Tada *et al.*[74]	100 (78F/22M)	No controls	68.0 (59.0, 76.0)	5.5 (1.2, 11.3) years	28% of patients diagnosed with sarcopenia (F: 26.9%; M: 31.8%).
Mochizuki *et al.*[75]	240 (189F/51)	No controls	75.0 ± 6.2	13.8 ± 11.1	29.6% of patients diagnosed with sarcopenia.
Feklistov *et al.*[76]	40F	40F controls	63 ± 7	NR	Sarcopenia occurred in 10 (25%) RA patients and in 5 (12.5%) people without RA (*p* > 0,05)
Kondrashov *et al.*[77]	110M	30 controls matched for age and BMI	59 (53; 65)	NR	Sarcopenia detected in 66 (60%) of RA patients, whereas in the control group it was absent.
Casabella *et al.*[78]	55F	55 controls	58 ± 12	NR	Nineteen RA patients (35%) presented sarcopenia
Park *et al.*[79]	294	No controls	NR	NR	8.2% of 294 RA patients had sarcopenia at the time of enrolment
El Maghraoui *et al.*[80]	178 (147F/31M)	No controls	54.1 ± 11.5	8.9 ± 7.4 years	53.9% of patients diagnosed with RC (F: 53.7% and M: 54.8%)
Engvall *et al.*[61]	60 (50F/10 M)	No controls	F: 66.0 (63.0–69.0) M: 60.0 (51.0–70.0)	F: 13 (9–23) years M: 16.0 16 (6–24) years	38% of patients categorized as having RC
Hugo *et al.*[81]	57 (41F/16M)	No controls	57.6 ± 10.2	3.8 ± 3.0 years	18% of patients categorized as having RC
Elkan *et al.*[82]	80 (61F/19M)	No controls	F: 60.8 (57.3–64.4) M: 63.4 (59.8– 66.9)	F: 6.0 (2.0–15.0) M: 5.0 (3.0–9.0)	18% of F patients and 21% of M patients categorized as having RC
Santo *et al.*[83]	90 (78F/12M)	No controls	56.5 ± 7.3	8.5 (3.0–18.0) years	13.3% of patients categorized as having RC

Results are expressed as mean ± standard deviation or median (25th–75th percentile).
ALM, appendicular lean mass; ALMI, appendicular lean mass index; BC, body composition; BMI, body mass index; F, female; FFM, fat free mass; FFMI, fat free mass index; FM, total fat mass; FMI, fat mass index; M, male; NR, not reported; PBF, body fat percentage; RA, rheumatoid arthritis; RC, rheumatoid cachexia; TLM, total lean mass.

the early RA patients and 19.8% of the controls were classified as having sarcopenia and 68.1% of the early RA patients and 47.3% of the controls were overfat.

Compared with healthy controls, patients with early RA exhibit alterations in body composition, with higher fat mass and lower lean mass leading to abnormal body composition conditions.

Established rheumatoid arthritis

We found five case-control studies ($n = 60$–189 cases) in which alterations in body composition were assessed in patients with established RA.[16,66–69]

In 2008, Giles et al.[16] reported alterations in body composition in a cohort of 189 RA patients (women: 62%; mean disease duration: 9 years; no previous exposure to bDMARDs: 55%). The RA patients were compared with non-RA controls matched for age, gender, weight and ethnicity. Weight, BMI and FM were significantly higher in women with RA (all $p < 0.05$), but not in men, compared with controls. No significant differences were found between men with RA and controls in any body composition parameter except for ALM, which was lower (24.7 *versus* 26.1 kg, $p = 0.039$). A significant association was found between RA status and greater prevalence of abnormal body composition conditions in women, but not in men; (i) sarcopenia (21.4 *versus* 7.7%, $p = 0.004$, using the criteria proposed by Janssen et al.[49]), (ii) overfat (57.3 *versus* 35.0%, $p = 0.001$, using the criteria proposed by Cesari et al.[47]) and (iii) sarcopenic obesity (11.1 *versus* 2.6%, $p = 0.008$).

These results were confirmed in most studies,[66–68] but not all.[69] Reina et al.[66] reported alterations in body composition in a case-control study of 89 women with RA (mean disease duration: 13.7 years). The control group was composed of 100 patients with non-inflammatory rheumatic disorders. TLM and ALM were significantly lower ($p < 0.001$) in RA patients compared with controls and no difference in FM was observed. RA patients fulfilled the criteria for sarcopenia in 44% of cases *versus* 19% of controls ($p < 0.001$, using the criteria proposed by Janssen et al.[49]). In a study of 60 RA patients (women: 83%; mean disease duration: 13 years; receiving DMARDs such as methotrexate, sulfasalazine, leflunomide and TNFα inhibitors: 68%). Elkan et al.[67]

reported higher FM ($p < 0.05$) both in women and men, and lower TLM ($p < 0.001$) in women (but not in men) compared with the reference population. In a case-control study, Lemmey et al.[68] compared 82 RA patients treated exclusively with csDMARDs (mainly methotrexate) in a treat-to-target (T2T) protocol with 85 matched controls. Although the RA patients responded well to the treatment (mean DAS28=2.8, with 49% in remission), they had lower ALM (−9.9%, $p < 0.001$) and higher FM (+26.5%, $p < 0.001$) than controls.[68]

Compared with controls, patients with established RA also have higher fat mass and lower lean mass leading to abnormal body composition conditions. Moreover, the benefits of the T2T strategy in reducing inflammation (i.e. disease activity) failed to improve body composition parameters.

Sarcopenia in patients with RA

We found ten cross-sectional studies ($n = 40$–457 RA patients) that specifically sought to evaluate the prevalence of sarcopenia in established RA.[70–79]

Although sarcopenia seems to be more frequent in RA patients compared with controls,[15,16,63,64,66] it is difficult to provide conclusive evidence since the studies used different definitions for sarcopenia and involved different populations. In a cross-sectional study of 123 Moroccan RA patients (women: 87%; mean disease duration: 9.8 years; patients receiving csDMARDs: 90.2%; patients receiving bDMARDs: 8.1%),[70] the prevalence of sarcopenia was reported to be 39.8% (using the criteria proposed by Baumgartner et al.[48]), but muscle strength and physical performance were not evaluated. In another cross-sectional study involving 82 patients with RA (women: 73.2%), Vlietstra et al.[71] found that the prevalence of sarcopenia (using the criteria proposed by Studenski et al.[55]) and sarcopenic obesity (using the criteria proposed by Gallagher et al.[85]) were 17.1% and 15.9% respectively. On the other hand, in a cross-sectional study of 388 consecutive women with RA, conducted by Torii et al.,[72] sarcopenia was defined as the presence of low muscle mass and either low muscle strength or low physical performance, as per the consensus report of the Asian Working Group for Sarcopenia (AWGS)[54] and 37.1% of the patients were classified as having sarcopenia.[72] In another cross-sectional study, Lin et al.[73] evaluated body composition

by BIA in 457 Chinese RA patients (women: 82.7%; mean age: 49.5 years) and found that low ALMI, with sarcopenia in 45.1% of the patients, using the AWGS criteria,[54] was the main characteristic of Chinese RA patients. In two other studies using BIA and the same criteria for sarcopenia,[74,75] the prevalence of sarcopenia among Japanese patients with RA was found to be 28% ($n=100$; mean age: 66.1 years; women: 78%) and 29.6% ($n=240$; mean age: 75.0 years; women: 78.8%), respectively.

The prevalence of sarcopenia in RA patients ranged from 17.1% to 60%, depending on the population that was evaluated and the assessment technique and diagnostic criteria that were used.

Rheumatoid cachexia
We found four cross-sectional studies[80–83] ($n=57$–178 patients) that specifically sought to evaluate the prevalence of RC using DXA and the criteria proposed by Engvall *et al.*[61]

As already mentioned, RC is another alteration in body composition observed in RA. Engvall *et al.* defined RC as FFMI < 10th percentile and FMI > 25th percentile.[61] The prevalence of RC ranged from 18% to 53.9%, depending on the cohort. El Maghraoui *et al.*[80] found the highest prevalence (53.9%), while Santo *et al.*[83] found the lowest prevalence (13.3%). Since this alteration in body composition is characterised by a loss of lean mass, RC is also associated with physical disability and mortality.[68]

The effect of treatments on body composition in patients with RA
Since body composition depends on several factors that can be potentially modified, this raises the question as to whether acting on these factors modifies body composition in RA. In this section, we investigate the effect of non-pharmaceutical treatments (i.e. nutrition and physical activity) and pharmaceutical treatments (i.e. corticosteroids and bDMARDs) on body composition in patients with RA. The results are summarized in Table 2.

Nutritional intervention
We found two small double-blind randomised placebo-controlled trials ($n=35$–40)[88,89] in which DXA was used to evaluate changes in body composition in RA patients 12 weeks after an anabolic nutritional intervention.

Wilkinson *et al.*[88] investigated whether anabolic nutritional supplementation could increase ALM. The participants were randomized to receive a drink containing either supplementary creatine ($n=15$) or placebo ($n=20$) for 12 weeks. A slight increase in ALM ($+0.52 \pm 0.13$ kg) was observed in the creatine supplementation group, while no significant changes were observed in the placebo group (between-group, $p=0.004$). Twelve weeks after cessation of the creatinine supplementation regimen, no significant differences in ALM were observed between the two groups. Other body composition parameters, such as FM, were not affected by creatine supplementation. Moreover, anabolic nutritional supplementation had no effect on muscle strength and physical performance, either immediately or 12 weeks after cessation of supplementation. In another study, Marcora *et al.*[89] compared the efficacy on body composition (with ALM as the primary outcome) of a mixture of β-hydroxy-β-methylbutyrate, glutamine and arginine (HMB/GLN/ARG) and a mixture of other non-essential amino acids used as placebo. At 12 weeks, the authors found no significant differences in ALM, or in any of the measured body composition parameters, between the intervention group and the placebo group.

The findings reported in these studies suggest that oral creatine supplementation induces a slight and temporary increase in ALM, with no changes in any of the other body composition parameters. However, due to the limitations of these studies (small number of patients and short period of time), no definitive conclusions can be drawn.

We found one small double-blind randomised placebo-controlled trial ($n=70$)[90] in which BIA was used to evaluate changes in BFP in RA patients 3 months after barberry extract (6 capsules of 500 mg per day). The results showed a slight decrease in BFP (-1.03 *versus* 0.37, $p=0.05$) in the intervention group compared with the placebo group. No lean mass measurements were performed.

Physical training
We found three small randomised controlled trials ($n=20$–100)[91–94] in which DXA was used to evaluate changes in body composition in RA

Table 2. Effect of nutrition, physical training and DMARDs on body composition in RA.

References	Type of study	Patients	Treatment	Mean age (years)	Disease duration	Conclusion
Wilkinson et al.[88]	24-week, double-blind, randomized, placebo-controlled trial	35 (15 in treatment group and 20 in placebo group)	Creatine supplementation: 20 grams (4×5 g/day) for the initial 5 days (loading dose) followed by 3 g/day for the remainder of the 12-week period (maintenance dose)	63.1 ± 10.0 years in creatine group	112.5 ± 82.8 months in creatine group	Significant increase in ALM in the creatine group (0.52 ± 0.13 kg), with no change in the placebo group (0.05 ± 0.13 kg); between-group $p = 0.004$). 12 weeks after cessation of supplementation, no significant difference in ALM or TLM between the two groups
				57.26 ± 10.4 years in placebo group	141.46 ± 160.1 months in placebo group	
Marcora et al.[89]	Randomized controlled trial	20 patients in supplementation group 20 in placebo group	b-hydroxy-b-methylbutyrate, glutamine and arginine for 12 weeks	54 ± 10	NR	At 12 weeks, no significant difference between the two groups
Aryaeian et al.[90]	Double-blind, randomized, placebo-controlled trial	31 patients in supplementation group 31 in placebo group	1500 mg barberry extract for 12 weeks	48.61 ± 11.69 in supplementation group 47.1 ± 10.75 in placebo group	NR	At 12 weeks, significant decrease in PBF in the supplementation group *versus* placebo group
Siqueira et al.[91]	Randomized, blinded, prospective, 16-week controlled trial	100 female patients (33 in land-based exercise group, 33 in water-based exercise group, and 34 in control group)	Water-based aerobic group	55 ± 6 in water-based exercise group 54 ± 5.1 in land-based exercise group 53.2 ± 7 in control group	9.2 ± 3.1 years in water-based exercise group 7.7 ± 2.9 years in land-based exercise group 8.5 ± 4 years in control group	No significant differences in total body composition (including body weight, lean or fat mass) in any of the groups during the period of intervention.
Marcora et al.[92]	Randomized controlled trial	10 patients in high-intensity progressive resistance training 10 patients in control group	High-intensity progressive resistance training	53 ± 13 in intervention group 54 ± 10 in control group	8.9 ± 5.7 years in intervention group 7.3 ± 5.3 years in control group	At 12 weeks, significant increase in TLM and significant decrease in PBF in the high-intensity progressive resistance training group compared with controls.
Lemmey et al.[93] Lemmey et al.[94]	Randomized controlled trial Follow up of the previous trial	13 patients in high-intensity progressive resistance training 15 patients in control group	High-intensity progressive resistance training	55.6 ± 8.3	74 ± 76 months	Significant increase in TLM ($p = 0.006$) and ALM ($p = 0.004$) in the high-intensity progressive resistance training group compared with controls. No difference between the two groups after 3 years of follow up
Cooney et al.[95]	Prospective study	10 patients (8F/2M)	8 weeks of exercise	64 ± 6	11 ± 12 years	Significant decrease in PBF

(continued)

Table 2. (continued)

References	Type of study	Patients	Treatment	Mean age (years)	Disease duration	Conclusion
Konijn *et al.*[96]	Ancillary study of COBRA-light (non-inferiority) trial	54 patients in COBRA-light group 54 patients in COBRA group	COBRA-light group (prednisolone 30 mg/day, tapered off to 7.5 mg/day in 8 weeks) COBRA group (prednisolone 60 mg/day, tapered off to 7.5 mg/day in 6 weeks)	51 ± 12 in COBRA-light group	20 (9–40) weeks in COBRA-light group	No difference between the two groups. Significant increase in total body and fat masses in all patients. However, no change in trunk/peripheral fat ratio
				54 ± 13 in COBRA group	16 (9–33) weeks in COBRA group	
Engvall *et al.*[17]	Controlled cross-sectional study	50 patients treated with prednisolone 50 patients never treated with prednisolone	Prednisolone	63 (56–68) in prednisolone group 64 (55–68) in control group	7.5 (4–12) years in prednisolone group 8 (5–18) years in control group	Significant increase in FM and PBF in prednisolone group compared with control group No difference in lean mass between the two group
Resmini *et al.*[97]	Case-control study	26 patients in RA 78 non matched controls	Low doses of prednisone (5 mg every day or 10 mg every 2 days)	62.0 ± 10.1 in RA group	NR	Significant decrease in TLM in RA group
Engvall *et al.*[98]	Ancillary study of Swefot (open, multicentre, randomised study)	22 patients in MTX-SLZ-HCQ group 18 patients in MTX-IFX group	To compare MTX-SLZ-HCQ *versus* MTX-IFX	59.5 (58.0–67.0) in MTX-SLZ-HCQ group 56.0 (42.0–73.0) in MTX-IFX	5.4 ± 2.9 months in MTX-SLZ-HCQ group 4.9 ± 3.4 months in MTX-IFX	Increase in fat mass (+3.77 kg, 1.63–5.90; $p = 0.040$) with infliximab at 24 months. Changes in lean mass did not differ significantly between the treatment groups
Marcora *et al.*[99]	Randomized phase II controlled trial	12 patients in ETN group 12 patients in MTX group	ETN	54 ± 11 in ETN group 50 ± 15 in MTX group	<6 months	At 24 weeks, only arm lean mass was significantly higher with etanercept compared with MTX
Serelis *et al.*[100]	Prospective study	19 F patients	TNFα inhibitors	54 ± 18	9 ± 7 years	At 1 year, no change in body composition
Toussirot *et al.*[18]	Single-centre, prospective, open-label study over 2 years	Eight patients with RA	TNFα inhibitors (IFX, ADA, ETN)	60.5 ± 3.4 in RA group	8.4 ± 2.5 years in RA group	In RA group, significant increase in BMI ($p = 0.05$), and trend towards significance for weight ($p = 0.07$) and visceral fat ($p = 0.059$).
Metsios *et al.*[101]	Prospective study	20 patients in treatment group 12 controls matched for age, sex and BMI	TNFα inhibitors	61.1 ± 6.8	17.3 ± 11.4 years	At 12 weeks, no significant change in body composition

(continued)

Table 2. (continued)

References	Type of study	Patients	Treatment	Mean age (years)	Disease duration	Conclusion
Tournadre et al.[102]	1 year open follow-up study	21 patients with RA 21 controls matched for age, sex, BMI and criteria for metabolic syndrome	Tocilizumab	57.8 ± 10.5	8.5 (1.7–21.5) years	At 1 year, significant gain in weight and BMI. In contrast, TLM, ALM and FFMI increased at 1 year. No change in VAT
Toussirot et al.[103]	Multicentre open-label study	107 patients (78F/29M)	Tocilizumab	56.6 ± 13.5	9.9 ± 8.1 years	No change in FM and PBF during the study
Vial et al.[104]	1-year open monocentric follow-up study	52 RA patients in TNFα inhibitors 23 RA patients in non TNFα inhibitors 21 RA patients in csDMARDs	TNFα inhibitor Non TNFα inhibitors csDMARDs	TNFα inhibitors: 56.9 ± 11.2 Non TNFα inhibitors: 56.9 ± 11.2 csDMARDs: 57.9 ± 10.8	TNFα inhibitors: 4.2 (1.6–12.0) Non TNFα inhibitors: 5.4 (2.3–14.8) csDMARDs: 0.3 (0.1–3.8)	TLM, FFMI and ALMI increased significantly in TNFα inhibitors group No change in body composition was observed in non TNFα inhibitors group No change in body composition was observed in csDMARDs group
Chikugo et al.[105]	3-month prospective study	8 female patients with RA	Tofacitinib *versus* bDMARDs	Tofacitinib: 55.3 ± 19.5 bDMARDs: 57.0 ± 14.7	8.5 ± 6.6 years in tofacitinib group 5.8 ± 10.8 years in bDMARDs group	At 3 months, body weight of patients in tofacitinib group tended to increase (p=0.06). Significant increase in PBF (p < 0.05), but no change in TLM. No change in body composition in bDMARDs group

Results are expressed as mean ± standard deviation or median (25th–75th percentile).
ADA, adalimumab; ALM, appendicular lean mass; ALMI, appendicular lean mass index; bDMARDs, biological disease-modifying anti-rheumatic drugs; BIA, bioelectrical impedance; BMI, body mass index; COBRA, combinatietherapie bij reumatoide artritis; csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; DXA, dual X-ray absorptiometry; ETN, etanercept; F, female; FFM, fat free mass; FFMI, fat free mass index; FM, total fat mass; FMI, fat mass index; HCQ, hydroxychloroquine; IFX, infliximab; M, male; MTX, methotrexate; NR, not reported; PBF, body fat percentage; RA, rheumatoid arthritis; SLZ, sulfasalazine; TLM, total lean mass; TNFα, tumour necrosis factor alpha; VAT, visceral adipose tissue.

patients 12–24 weeks after a physical training intervention.

Siqueira *et al.* randomized 100 women with RA to three groups: one with land-based exercises, one with water-based exercises and one without exercise (control group). After 16 weeks, no significant changes in body composition or in muscle strength were observed between the groups.[91] In a pilot trial, 10 patients participating in a supervised progressive resistance training (PRT) program were compared with 10 patients with no training program. At 12 weeks, a significant gain in TLM (primary outcome) ($+1.2$ kg, $p = 0.005$) and a significant loss of PBF (-1.1%, $p = 0.047$) were observed.[92] Moreover, it was the increase in ALM that accounted for the significant increase in lean mass; changes in body composition were found to be associated with improvements in various physical function parameters.[92] In a randomised controlled trial involving 28 patients, Lemmey *et al.* confirmed the efficacy of high-intensity PRT in restoring muscle mass and function in patients with RA.[93] At 24 weeks, the authors observed a significant gain in TLM ($+1.5$ kg, $p < 0.01$) and ALM ($+1.2$ kg, $p < 0.01$) in the high-intensity PRT group, but no changes in the control group (home-based range of movement exercise).[93] In a 3-year follow-up study, the authors reported that long-term resumption of normal activity resulted in the loss of PRT-induced improvements in lean mass and strength-related function.[94] In a small prospective non-controlled study assessing 8 weeks of exercise (aerobic exercise followed by PRT 3 times per week) in 10 RA patients (eight women; age 64 ± 6 years; disease duration 11 ± 12 years), a significant decrease in PBF assessed by BIA was found (-9%).[95] No lean mass measurements were performed.

The findings reported in these physical training intervention studies demonstrate that PRT improves lean mass and physical function.

Corticosteroids

Chronic exposure to corticosteroids is known to induce cushingoid appearance and weight gain.[106] Despite this, corticosteroids are recommended at the beginning of treatment for RA, but only as a short-term treatment. They should be tapered off as quickly as clinically feasible.[107]

We found three studies (one prospective study and two cross-sectional studies)[17,96,97] in which DXA was used to evaluated changes in body composition (particularly fat mass and redistribution) in RA patients following corticosteroid treatment.

In a prospective study, Konijn *et al.* investigated the effects of two different high-dose, step-down prednisolone regimens on body composition in early RA patients after 26 weeks of treatment. This study was part of the larger multicentre COBRA-light trial (*Combinatietherapie Bij Reumatoide Artritis*), which assessed the non-inferiority of COBRA-light therapy (prednisolone 30 mg/day, tapered off to 7.5 mg/day in 8 weeks, and methotrexate (MTX) escalated to 25 mg/week in 8 weeks) *versus* COBRA therapy (prednisolone 60 mg/day, tapered off to 7.5 mg/day in 6 weeks, MTX 7.5 mg/week and salazopyrine 2 g/day). Overall, 108 patients were evaluated ($n = 54$ in each group). All patients exhibited a significant increase in total body and fat mass (TBM $+1.6$ kg, $p < 0.001$ and FM $+1.3$, $p < 0.001$ respectively). Surprisingly, no changes in fat redistribution (trunk/peripheral fat ratio) were observed.[96] No significant changes in lean mass (total and appendicular) were observed in either group. In a cross-sectional study, body composition was assessed by DXA in 100 RA patients (50 women) with a median [interquartile (IQR)] disease duration of 8 (4–15) years. Fifty had been treated with prednisolone (5–7.5 mg) for at least 2 years and 50 gender- and age-matched patients had not. A significant increase in FM and PBF was observed in the prednisolone group compared with the control group, but no significant differences in fat redistribution and TLM were observed between the two groups.[17] In another study, body composition was evaluated after endogenous (Cushing's syndrome) and exogenous (RA women, $n = 26$) exposure to glucocorticoids (5 mg of prednisone every day or 10 mg every 2 days).[97] However, due to the study design, no definitive conclusions could be drawn.

The findings reported in these studies demonstrate that exposure to corticosteroids increases total body and fat mass but, surprisingly, induces no changes in fat redistribution and lean mass.

Biologic disease modifying anti-rheumatic drugs

Individually-tailored treatment strategies featuring early and aggressive DMARDs use and frequent monitoring of treatment response to

achieve low disease activity (preferably clinical remission) form the cornerstone of pharmacological treatment in RA.[107] Conventional synthetic DMARDs are recommended as part of the first-line treatment strategy.[107]

To date, no studies have been published that have specifically sought to investigate the effect of csDMARDs on body composition in RA patients. Biologic DMARDs are considered if the response to csDMARDs is insufficient or if the latter are contraindicated.[107] Most of the data on body composition were from studies on TNFα inhibitors.

We found two randomised controlled trials[98,99] and four small prospective studies[18,100,101] in which the effect of TNFα inhibitors on body composition in RA patients was assessed, mainly using DXA.

Engvall *et al.* investigated 40 early-RA patients in whom treatment with methotrexate (MTX) at a dose of up to 20 mg/week for 3 months had failed. The patients were randomised to an 'addition of sulfasalazine and hydroxychloroquine' group ($n = 22$) or an 'addition of TNFα inhibitors (infliximab)' group ($n = 18$). At 24 months, a significant increase in FM was observed in the infliximab treatment group (+3.8 *versus* +0.4 kg, $p = 0.04$), while changes in lean mass (both ALM and TLM) did not differ significantly between the two groups.[98]

Marcora *et al.* conducted a study to assess the effect of etanercept on body composition. Twenty-four patients with early RA (disease duration <6 months) were randomized to two groups. In one group, the patients were treated with etanercept ($n = 12$) and in the other with MTX ($n = 12$). At 24 weeks, no significant changes in body composition were found.[99] Similar findings (i.e. no significant changes in body composition) were reported with TNFα inhibitors in three small prospective studies ($n = 8$–20) with various follow-up intervals (12 weeks to 2 years) and without control groups.[18,100,101] On the other hand, in a 1-year open follow-up study involving 83 RA patients (75% women; mean age 58.5 years; median disease duration 3.7 years), Tournadre *et al.*[104] found significant changes in lean mass parameters in patients treated with TNFα inhibitors. In that study, the body composition parameters of 47 bDMARDs-naïve patients (mainly etanercept, $n = 35$) with active RA were compared with those of patients treated with csDMARDs alone ($n = 18$)

or with non-TNFα inhibitor bDMARDs ($n = 18$ including 2 with tocilizumab, 10 with rituximab and 6 with abatacept). No significant difference in BMI changes over time was observed in any of the treatment group. After 1 year of TNFα inhibitors, lean mass as assessed by TLM ($p = 0.015$), FFMI ($p = 0.013$) and ALMI ($p = 0.010$) increased significantly and was associated with an improvement in muscle function and strength. No change in body composition was observed at 12 months in patients treated with non-TNFα inhibitor bDMARDs or csDMARDs.[104] However, due to the lack of randomisation and the small sample size of the controls, no definitive conclusions can be drawn. Moreover, 45% of patients were on steroids (median dose 6.5 mg/day) with a heterogeneous distribution between the groups (72.2% in the non-TNF inhibitor bDMARDs group *versus* 38.3% in the TNF inhibitor groups *versus* 33.3% in the csDMARDs group).

In two open, prospective 1-year follow-up studies, treatment with the interleukin-6 (IL-6) inhibitor, tocilizumab, was reported to be associated with a gain in lean mass, but with no change in fat mass.[102,103]

Tournadre *et al.*[102] investigated the effect of tocilizumab on body composition in 21 patients with RA.[2] At baseline, the patients were compared with 21 controls matched for age, sex, BMI and metabolic syndrome criteria. After 1 year of treatment with tocilizumab, the authors observed a significant gain in weight and BMI (+1.9 kg, $p < 0.01$ and +1.2 kg/m², $p < 0.01$ respectively). Significant gains in ALM and TLM were observed at 12 months (+1.0 kg, $p < 0.001$ and +1.1 kg, $p < 0.05$ respectively). In contrast, no changes in FM were observed.[104] These findings in respect of lean mass were recently confirmed in a French multicentric study (the ADIPRAT study) conducted by Toussirot *et al.*[103] In that study, the authors assessed 107 RA patients who had begun treatment with tocilizumab. BC was evaluated by DXA at baseline and at 6 and 12 months. Significant increases in TLM were observed at 6 and 12 months (+1.0 kg, $p = 0.01$ and +1.3 kg, $p = 0.02$ respectively). Fat parameters did not change over time.

IL-6 is a myokine (i.e. a cytokine produced and released by myocytes under the action of contractile activity).[108] During exercise, its secretion induces an increase in the production of hepatic glucose, which serves as an energy source for contracting muscles. IL-6 also mediates the crosstalk
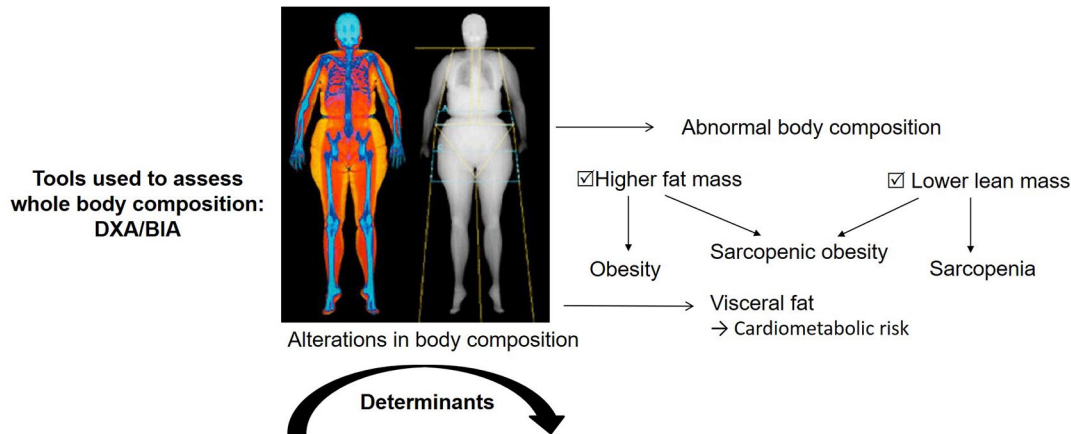
Figure 1. Body composition alterations in rheumatoid arthritis.

between insulin-sensitive tissues.[108] However, chronic exposure to IL-6 has been reported to be associated with muscle atrophy.[109] Inhibition of IL-6 attenuates muscular atrophy and dystrophy in several preclinical models.[110,111]

There are no data available on the effect of other bDMARDs (such as abatacept or rituximab) on body composition in RA patients. Data on JAK inhibitors are too scarce to draw any definitive conclusions on their effect on body composition.[105]

Patients with RA exhibit a significant loss of lean mass and a significant gain in fat mass (Figure 1). The use of TNF inhibitors might be associated with a further gain in fat mass with no major change in lean mass, while the use of the IL-6 inhibitor, tocilizumab, might be associated with a gain in lean mass with no further change in fat mass. However, there are limitations to the studies that sought to investigate the effect of tocilizumab, most notably the small number of patients, no randomization and no assessment of nutritional status and physical performance.

Limitations
Alterations in body composition in RA patients is a growing field of interest. However, there are several limitations to the studies we reviewed. Firstly, only four studies focused on patients with early RA. As a result, few conclusions can be drawn. In addition, in three of the four studies, the number of patients was small (less than 150). Moreover, the prevalence of sarcopenia in RA patients is difficult to estimate since different criteria were used to define sarcopenia. Further

studies are needed with the new EWGSOP criteria, which assess muscle function, mass and strength.[19] Interventional studies are also lacking, especially on the effect of nutrition, exercise, corticosteroids and DMARDs on body composition in patients with RA. The studies assessing bDMARDs also lack statistical power, as few patients were included (less than 100 patients), limiting the conclusions that could be drawn.

Conclusion
In this review we identified several clinical studies on the assessment of and alterations in whole-body composition in patients with RA. However, the studies had several methodological limitations due to inconsistent definitions of altered body composition conditions. The findings reported in the studies demonstrate that (i) RA is characterized by alterations in body composition, and specifically a loss of lean mass and a gain in adiposity compared with healthy controls, regardless of sex, (ii) the prevalence of abnormal body composition conditions, such as overfat, sarcopenia, sarcopenic obesity and RC, is significantly higher in RA patients and (iii) these alterations in body composition are observed even at an early stage of the disease (i.e. before initiation of DMARDs).

Data on the effect of nutritional intervention, physical training and treatments (i.e. corticosteroids and bDMARDs) on body composition in RA patients are scarce. The findings reported in the studies demonstrate that (i) creatine supplementation and PRT programs induce a slight and temporary gain in lean mass, (ii) exposure to corticosteroids induces a gain in fat mass and (iii) the use of TNF

inhibitors might be associated with a gain in fat mass, while the use of tocilizumab might be associated with a gain in lean mass.

Longitudinal studies are needed to evaluate whether alterations in body composition are more pronounced in RA patients compared with controls. There are still many gaps in our understanding of the alterations in body composition that occur in RA patients, including their initiation and progression, their determinants and outcomes and their treatment.

Authors' note
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Author Contributions
Conceptualization: J.G.L. and J.P.; methodology: J.P.; writing: original draft preparation: J.G.L.; writing: review and editing: J.P., R.M.F, AT and B.C.; visualization, J.P., R.M.F, A.T. and B.C.

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The authors declare that there is no conflict of interest.

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