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Effect of biological disease-modifying antirheumatic drugs on body composition in patients with rheumatoid arthritis: a systematic review and meta-analysis

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Abstract

Background: Rheumatoid arthritis (RA) generates an inflammatory profile that predisposes to total and visceral fatty accumulation and reduced fat free mass (FFM). This metabolic disorder contributes to poor functionality, increased cardiovascular risk and higher mortality. This study aimed to address a systematic review with meta-analysis to determine the effect of biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs) on body composition (BC) of patients with RA.

Methods: The search was conducted at the electronic databases PubMed, Cochrane Library, Embase, Lilacs and grey literature. This investigation was carried until July 2021. Outcomes of interest were total weight, body mass index (BMI), fat mass (FM) and FFM. A meta-analysis comparing these outcomes in RA patients under bDMARD treatment *versus* controls was performed.

Results: Out of 137 studies reviewed, 18 were selected: fifteen prospective cohorts, two retrospective cohorts, and one cross-sectional study. The studies comprised 1221 patients, 778 on bDMARD treatment and 443 controls, which included RA patients under conventional synthetic DMARD (csDMARD). No study addressing BC analysis in patients using tsDMARD was found. The mean age and duration of the disease was 56.7 years and 6.77 years, respectively. Ten studies demonstrated a significant increase of total weight in 88.2% of patients and 42.3% for BMI. In studies that analyzed BC by double X-ray absorptiometry (DXA), the increase in total weight and BMI correlated positively to the increase in FFM. The meta-analysis carried out in five studies showed no significant difference of the mean difference for total weight 0.12 kg (95% CI − 5.58, 5.82), BMI 0.08 kg/m^2 (95% CI − 1.76, 1.92), FM − 0.08 kg (95% IC − 5.31, 5.14), and FFM − 2.08 kg (95% CI − 7.37, 3.21).

Conclusion: This systematic review suggests a possible impact of bDMARDs on BC of RA patients, even though, the meta-analysis carried out in a small part of these studies was not able to confirm significant variation in BC components.

Trial registration: PROSPERO code: CRD42020206949.

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Keywords: Rheumatoid arthritis, Body composition, Disease-modifying antirheumatic drugs, Rheumatoid cachexia, Fat free mass

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects characteristically the synovium joints. Systemic manifestations may also occur, along with an inflammatory profile that predisposes to the accumulation of total and visceral fat, reduced fat free mass (FFM), reduced functionality and increased cardiovascular (CV) risk and mortality [1–4]. The reduced FFM associated with stable or increased fat mass (FM) is denominated rheumatoid cachexia (RC) [5]. The RC is difficult to diagnose, as most patients have stable or high total body weight, especially when associated with obesity, making body mass index (BMI) a method with low accuracy for RA patients [5]. The frequency of obesity can reach 60% in RA patients, and a Brazilian study showed a prevalence of 26.9% [2, 3].

Santo et al. [6] demonstrated in a systematic review with meta-analysis that the prevalence of RC in RA patients was 15–32% according to different criteria. Both RC and obesity are associated with poor CV, functional and disease outcomes in RA population, reinforcing the importance of body composition (BC) assessment [1, 4]. There is no evidence that modifying BC in RA patients will improve functional outcomes and reduce CV morbidity and mortality; however, extrapolating from the general population knowledge, an increase in FFM and a reduction in fat proportion could have beneficial effects on CV risk and quality of life in RA patients [3, 4].

Biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs) were revolutionary in RA treatment, reducing drastically inflammation, bone erosions, and improving quality of life. Even though the impact of bDMARDs and tsDMARDs on BC is controversial and not totally elucidated. The control of disease activity reduces inflammation but less frequently influences RC [3, 4, 7].

In this context, this systematic review with meta-analysis aimed to address the effect of bDMARDs and tsDMARDs on BC in patients with RA.

Methods

This systematic review with meta-analysis was based on recommendations from the Cochrane Guidelines for Systematic Reviews and was written according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8]. The registration was approved in PROSPERO (CRD42020206949).

Search strategy

To identify studies that assessed the effects of DMARDs on BC in RA patients we searched through the acronym PECO (population, exposure, comparison, and outcome), four independent databases to perform the sensitive literature search: PubMed (Medline), Embase, Cochrane Library (Central) and Lilacs. Additionally, we searched for grey literature including American College of Rheumatology (ACR) and European Alliance of Associations for Rhrumatology (EULAR) abstracts.

There was no language, date, document type, or publication status limitations for inclusion of records. The research of information was conducted until July 2021. Descriptors were identified in Medical Subject Headings (MeSH), *Descritores em Ciências da Saúde* (Decs) and Embase Subject Headings (Emtree). The research strategy was adapted based on descriptors in each database and are presented as supplementary materials at Additional file 1.

Studies selection and data extraction

We uploaded electronic search results from defined databases to the Rayyan Qatar Computing Research Institute [Rayyan] [9]. Two authors independently screened titles and abstracts and subsequently, assessed each study to determine whether it met the inclusion criteria. A third reviewer evaluated the disagreements.

Studies were selected comprising the inclusion criteria of individuals above 18 years old that fulfilled the 1987 ACR or 2010 ACR/EULAR classification criteria for RA; starting or under treatment with agents including bDMARD or tsDMARD; with assessment of BC by BMI, anthropometry, or double X-ray absorptiometry (DXA), comparing two different times (baseline and follow-up) and/or comparing to control group.

Duplicated studies, narrative review, integrative review, letters, systematic reviews, and meta-analysis, absence of full text that did not present the necessary information at the abstract, divergent targets, experimental studies, children and/or adolescents, and exclusive immune-mediated rheumatic diseases other than RA or use of other drugs than bDMARD or tsDMARD were excluded.

The following information was extracted: study design, follow-up duration, sample size, gender distribution, menopause status, DMARD type, control group, age, duration of disease, positivity by

rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP), glucocorticoid use, smoking, physical activity (PA) and diet pattern, disease activity score in 28 joints (DAS28), type of BC assessment, frequency of assessment; and the key outcomes as weight, BMI, FM and FFM.

Quality assessment

Two investigators independently assessed the risk of bias in the selected studies according to the Newcastle–Ottawa Scale (NOS). A third reviewer evaluated the disagreements. Possible sources of bias in a cohort study include eight items related to selection, comparison, and outcome. The cohort studies with six stars (maximum of nine) were classified as good quality. For cross-sectional studies, the modified version of NOS, studies that received at least seven stars (maximum of ten) were classified as good quality.

For the randomized studies, the risk of bias was assessed according to the Jadad Scale (also known as the Oxford quality scoring system) that consists of three items: randomization, blinding and description of patient withdrawals/dropouts. From a total of five points, a Jadad score of zero to two indicates that the study is of low quality, whereas a score of three to five indicates a study of high quality [10].

Statistical analysis

A meta-analysis comparing BC in RA patients under bDMARD treatment *versus* controls was performed. The results of each selected study were presented as mean differences with their 95% confidence interval. Meta-analyses were carried out using the inverse variance method, pooling estimates of each study using fixed or random effect model according to the level and significance of heterogeneity. Heterogeneity was tested with Cochrane's Q-test and evaluated by the I^2 statistic, (I^2 25%, 50% and 75%, considered low, moderate, and high heterogeneity respectively). For the Q-test, a p-value < 0.10 was considered significant and a random-effect model was used. The analysis was performed using RevMan 5.1.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). *P*-values less than 0.05 were considered statistically significant.

Results

This research retrieved 137 studies; 13 registers were excluded for duplicates. A hundred and six studies were discarded after title and abstract analysis, five had no full-text available nor the necessary information in the abstract, and 13 were selected for full-text screening. Additional ten studies were identified through grey literature and were included in the screening, totalizing 23 studies. After full-text reading, three studies were excluded for different outcomes, one was an observational study and one was the same cohort as another study. Therefore, 18 studies were eligible for inclusion in this systematic review [11–28]. The flowchart of eligibility was presented at Fig. 1.

Design, year of publication and quality of the studies

The selected studies were published between 2006 and 2021, nine (50%) published in the last 5 years [11–28]. Fifteen (83.5%) articles included were prospective cohorts [11–13, 15–17, 19–21, 23–28]; two (11%) of them being randomized clinical trials [12, 19]. Two (11%) studies were retrospective cohorts [14, 22] and one (5.5%) had a cross-sectional design [18].

Considering the NOS, the mean quality result for the cohort studies was 7.15 and for the single cross-sectional study it was 10. The result of NOS is presented as Table 1.

Considering the Jadad Scale (Oxford quality scoring system) for randomized studies, the mean quality result was 3.5 points, which indicates a high quality [10]. The result of Jadad Scale is presented as Table 2.

Conflict of interest

The authors of two studies have received personal fees or research support from pharmaceutic industry, but not related to the submitted work [27, 28]. Three studies were funded by pharmaceutic companies [20, 21, 23], and another one was a sub analysis of a tocilizumab trial [22].

Characteristics of the patients and medications

Data from a total of 1221 patients were available, 778 of those were RA patients starting or under treatment with bDMARD and 443 were controls. The intervention group was represented by 512 patients treated with tumoral necrosis factor inhibitor (TNFi) (279 etanercept, 121 adalimumab, 87 infliximab, 9 certolizumab pegol, 8 golimumab, 8 unspecified); 241 using interleukin 6 receptor inhibitor (anti-IL6) (tocilizumab) and 15 using inhibitor of co-stimulation of T cells (abatacept), 10 using antibody against CD20 protein (rituximab). The number of participants in each study using bDMARD ranged from eight to 167, and all the bDMARDs were used at standardized dosage.

The control group was represented by 205 RA patients using conventional synthetic DMARD (csDMARD) including methotrexate, sulfasalazine, hydroxychloroquine or leflunomide; 177 healthy controls; 28 osteoarthritis individuals, 12 ankylosing spondylitis patients and 21 patients with metabolic syndrome. One study that evaluated TNFi effect on BC had the control group composed by patients using rituximab, abatacept and tocilizumab [28].

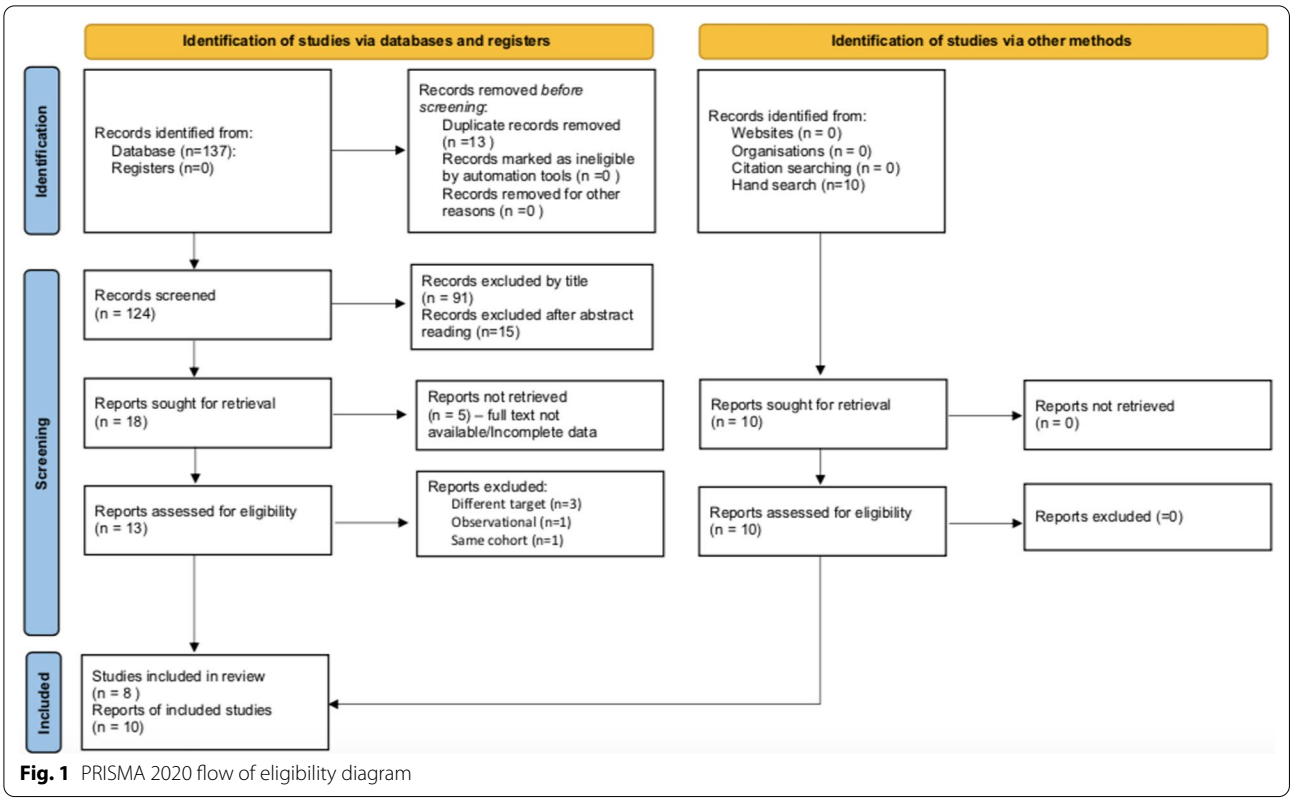

Fig. 1 PRISMA 2020 flow of eligibility diagram

Table 1 Quality assessment of studies by Newcastle–Ottawa Scale

References	Selection	Comparability	Outcome	Overall quality
NOS cohort				
Serelis et al. [11]	***	–	***	6
Kopec-Medrek et al. [15]	***	*	***	7
Toussirot et al. [16]	***	*	***	7
Tournadre et al. [23]	***	–	***	6
Van den Oever et al. [20]	***	*	***	7
Toussirot et al. [21]	***	–	***	6
Hasegawa et al. [27]	***	–	***	6
Vial et al. [28]	****	**	***	9
Metsios et al. [24]	***	–	**	5
Ferraz-Amaro et al. [13]	****	**	***	9
Chih-Yen Chen et al. [25]	****	**	***	9
Brown et al. [14]	***	–	***	6
Sfriso et al. [17]	****	**	***	9
Chapman et al. [26]	***	–	***	6
Choi et al. [22]	****	**	***	9
NOS transversal				
Ramos et al. [18]	*****	**	***	10

NOS, Newcastle–Ottawa Scale

Each star means the fulfillment of a study quality criteria and can be assigned in cohort studies, maximum of 9 (selection 0–4; comparability 0–2; outcomes 0–3) and for cross-sectional studies maximum of 10 (selection 0–5; comparability 0–2; outcomes 0–3)

Each "*" is one star counting in the score

Table 2 Quality assessment of studies by Jadad scale (Oxford quality scoring system)

References	Randomization	Blinding	Withdrawal	Total
Marcora et al [19].	**	*	*	4
Engvall et al. [12]	**	-	*	3

Each star means the fulfillment of a study quality criteria and can be assigned to randomized cohort studies a maximun of 5 (randomization 0–2; blinding 0–2; withdrawal 0–1)

Each "*" is one star counting in the score

Prednisone use was reported by 11 (61%) studies, with the mean value of 6.23 mg/day before intervention and 3.79 mg/day at the end of follow up. Four (22%) studies informed absence of prednisone use, and three (16.5%) did not mention this information.

No study with RA patients using tsDMARD and addressing BC analysis was found in our search.

Distribution by age, gender, menopause status and smoking

The mean age was 56.7 years, and the female proportion ranging from 37.5 to 100% of the sample. Four (22%) studies reported the postmenopausal status, ranging from 25 to 100% of the women. Smoking rate was presented in nine (50%) studies, ranging from 0 to 54.5%.

Disease duration and seropositivity for rheumatoid factor and anti-cyclic citrullinated peptide

The mean disease duration was 6.77 years and the mean follow up in the studies was 13.1 months. Eleven (61%) studies informed RF or anti-CCP status, with a mean result of 67.4% of positivity. The DAS28 was evaluated in all studies, with mean value of 4.89 at baseline and 2.98 after intervention, showing significant decrease in 15 (83.5%) studies.

Physical activity and diet

Nine (50%) studies evaluated PA, and five (55.5%) of them reported it as regular, absent, or less than three hours/week of exposure. One study mentioned a natural increase in PA after intervention. Three (33%) studies quantified PA during the intervention and two showed a significant improvement in the ten meter walking test ($p=0.002$), Health Assessment Questionnaire (HAQ) score ($p<0.001$) [27], and in the six minutes walking test or handgrip test ($p<0.001$) [28].

Diet was evaluated in eight (44.5%) studies, five (62.5%) of them reported patients having a regular diet, with no detailing, and two informed prohibitions of protein supplementation. One mentioned a natural increase of protein intake, and two assessed and classified diet but without intervention during the follow up [17, 24, 27].

Body composition

Fourteen (78%) studies comprising 718 patients analyzed BC by BMI [11–13, 15–18, 20, 21, 23–26, 28], ten (55.5%) by DXA (324 patients) [11, 12, 15, 16, 19–21, 24, 27], three (16.5%), by bioimpedance (77 patients) [13, 24, 25] and one (5.5%) by skin folder measure (21 patients) [18]. In some studies, more than one method of BC evaluation was performed. Results were obtained by a comparison from baseline to a minimum of three and a maximum of 24 months, with a median of 12 months. Data of the studies are summarized in Table 3.

Body weight and body mass index

Thirteen (72%) studies evaluated body weight, comprising 633 patients. Eight (61.5%) of these studies, representing 558 (88.2%) patients, showed a significant mean increase of 1.63 kg [13, 14, 17, 21–23, 25, 27], two (15.5%) studies showed a tendency of increase with no statistical significance [15, 16] and three (23%) did not show change in body weight [11, 19, 24]. Six studies did not assess this outcome [12, 18, 20, 26, 28, 29].

Among the fourteen (78%) studies that analyzed BMI, comprising 451 patients, six (43%) of them, representing 191 (42.3%) of the patients, showed a significant increase of 0.94 kg/m^2 [13, 16, 21, 23, 25, 26], and eight (57%) did not show any change in BMI [11, 12, 15, 17, 18, 20, 24, 28].

Among the four (22%) studies designed with anti-IL6 intervention, comprising 234 patients [21–23, 26], three (75%) of them, representing 128 (54.7%) of the patients, demonstrated a significant increase in total weight of 1.2 kg [21–23] and also three (75%), representing 127 (62.8%) of the patients showed an increase in BMI of 0.83 kg/m^2 [21, 23, 26].

In summary, among the eighteen studies, included in the analyses, ten (55.5%) of them, representing 585 (75.2%) of the patients, showed a significant increase in body weight or BMI. No change in body weight and BMI was reported in the control group.

Body composition by double X-ray absorptiometry

Among the ten studies, comprising 324 patients that analyzed BC by DXA [11, 12, 15, 16, 19–21, 23, 27, 28], three (33,5%) of them, representing 176 (54.3%) of the patients, showed a significant increase in body weight [21, 23, 27] and three (33.5%), representing 136 (42%) of the patients in BMI [16, 21, 23]. In the assessment of specific

Table 3 Characteristics of studies and body composition in rheumatoid arthritis patients under bDMARDs treatment

References	Study design	Total N	No of patients/ intervation	No of patients/ control	Duration	Age (mean)	BC assessment	Total Weight kg before/after (SD)	BMI before/after (SD)(CI)***	FM kg /or %* before/after (SD)	FFM kg before/ after (SD) (CI)***
Marcora et al. [19]	Prospective Rand Cohort	26	12 TNFi	14 RA MTX	6	52	DXA	76.4 (14.4) 77.5 (16.1)	28.0 (7) na	31.7 (8.2) 32.3 (8.5)	43.8 (10) 44.3 (10.9)
Serelis et al. [11]	Prospective Cohort	19	19 TNFi	no	12	54	DXA	69.5 (12.6) 69.8 (12.6)	26.1 (4.98) 26.3 (4.12)	28.4 (10.1) 28.5 (10.2)	39.7 (7.4) 39.8 (7.3)
Engvall et al [12].	Prospective Rand Cohort	40	18 TNFi	22 RA csDMARD	21	57.7	DXA	na	24.7 (3.7) Δ + 0.89	**24.4 (7.5) Δ + 37.7****	45.9 (9.4) Δ + 570
Kopec-Medrek et al. [15]	Prospective Cohort	32	16 TNFi	16 healthy	14	na	DXA	69.2 (3.64) 70.8 (3.44)	26.0 (1.29) 26.6 (1.23)	**26.7 (2.9) 28.0 (2.6)****	40.2 (1.46) 40.5 (1.07)
Toussirot et al. [16]	Prospective Cohort	20	8 TNFi	12 AS TNFi	24	60.5	DXA	66.4 (4.4) 67.5 (4.3)	**23.4 (0.73) 24.1 (0.8)****	18.6 (1.8) 20.0 (1.8)	46.0 (4.2) 45.8 (4.3)
Tournadre et al. [23]	Prospective Cohort	42	21 TCZ	21 Met. Syndrome	12	57.8	DXA	**61.8 (19.3) 63.7 (16.1)****	**23.6 (6.7) 24.8 (5.9)****	19.5 (1.2) 19.5 (9.5)	**42.1 (1.1) 43.2 (1.1)****
Van den Oever et al. [20]	Prospective Cohort	56	28 TNFi	28 OA	6	54	DXA	na	26.2 (4.0) 25.7 (3.5)	37% (11)* 37% (11)*	46.1 (7.6) 46.7 (7.7)
Toussirot et al. [21]	Prospective Cohort	107	107 TCZ	No	12	56.6	DXA	**70.3 (15.1) 72 (15.3)****	26.4 (5.5) 27.2 (5.8)	27.7 (12.1) 28.1 (1.1)	**40.7 (8.4) 42.1 (8.9)****
Hasegawa et al. [30]	Prospective Cohort	48	34 TNFi, 9ABT, 5TCZ	No	12	64.2	DXA	**54.6 (12.4) 55.8 (13.6)****	na	na	**5.1 (0.5)# 5.3 (0.7)****
Vial et al. [28]	Prospective Cohort	83	47 TNF	18 csDMARD 10 RTX, 6 ABT, 2 TCZ	12	58.5	DXA	na	26.7 (6.4) 27.0 (6.5)	25.3 (12.2) 25.4 (11.5)	**49.6 (10.8) 50.7 (11.3)****
Metsios et al. [24]	Prospective Cohort	32	20 TNFi	12 healthy	3	60	Bioimp	79.4 (15.6) 78.8 (16.6)	28.3 (3.7) 28.1 (4.1)	38.8% (7.5)* 36.0% (7.4)*	50.9 (12.7) 51.1 (12.5)
Ferraz-Amaro et al. [13]	Prospective Cohort	120	16 TNFi	34 AR csDMARD 70 healthy	12	53.6	Bioimp	**72.0 (14.0) 73.9 (13.7)****	**26.9 (3.88) 28.0 (4.57)****	19.8 (7) 22.0 (9.7)	53.7 (48.7–62.3)*** 50.5 (44.2–58.5)
Chin-Yen Chen et al. [25]	Prospective Cohort	30	20 TNFi	10 RA csDMARD	12	54.7	Bioimp	**55.8 (10.6) 57.7 (11.3)****	**22.0 (3.2) 22.8 (3.6)****	29.5% (5.8)* 30.7% (6.0)*	na
Ramos et al. [18]	Transversal	123	21 TNFi	23 RA csDMARD 79 healthy	48	54.8	Skin fold	na	28.1 (25–31)*** na	na	na
Brown et al. [14]	Prospective Cohort	168	168 TNFi	no	24	63.8	BMI	**75.3 (17.59) Δ + 1.80****	26.5 (5.19) na	na	na
Sfriso et al. [17]	Prospective Cohort	131	91 TNFi	40 RA MTX	24	59.9	BMI	**62.2 Δ + 2.4****	23.25 na	na	na
Chapman et al. [26]	Prospective Cohort	19	19 TCZ	no	6	49.6	BMI	na	**25.5 (21–32)*** 26.0 (21–32)****	na	na
Choi et al. [22]	Prospective Cohort	131	87 TCZ	44 RA MTX	6	52.8	BMI	**53.4 (8.6) 4.3 (8.4)****	22.6 na	na	na

Data in bold showed statistical significance

ABT, abatacept; csDMARD, conventional synthetic disease modifying antirheumatic drug (englobing: MTX, methotrexate; SSZ, sulfasalazine; LFN, leflunomide; HCQ, hydroxychloroquine); RTX, rituximab; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitos (englobing: ADA, adalimumab; ETN, etanercept; IFX, infliximab; CZP, certolizumab pegol; GOL, golimumab). AS, ankylosing spondylitis; Bioimp, bioimpedance; BMI, body mass index; Met. Syndrome, metabolic syndrome; na, not available; OA, ostheoarthritis; RA, rheumatoid arthritis; Bioimp, bioimpedance; BMI, body mass index; BC, body composition; DXA, dual X-ray absorptiometry; FFM, fat free mass; FM, fat mass; na, not available; SD, standard deviation

*Data available in percentage; ** p-value < 0.05; ***CI: confidence interval; # muscle index in sarcopenic group

components of BC, four (40%) studies, representing 223 (68.9%) of the patients, showed a significant increase in the FFM in the intervention group [21, 23, 27, 28] and two (20%), representing 34 (10.5%) of the patients, showed a significant increase in the FM [12, 15].

Even though it was not significant, in the three studies that showed an increase in total weight, and, in two of the studies that showed an increase in the BMI, there was a positive correlation with the increase in FFM, without variation on FM [21, 23, 27]. One study [12] showed an increase in FFM in the control group.

Body composition by bioimpedance and skin fold

Among the four studies, comprising 77 patients that analyzed BC by bioimpedance or skin fold [13, 18, 24, 25], two (50%, 36 patients) of them showed a significant increase in total weight and BMI [13, 25], but none of them showed a variation in FM and FFM.

Meta-analysis

As a result of heterogeneity of BC evaluation, five studies could be meta-analyzed including 194 patients [19, 20, 22, 25, 28].

The analysis comparing RA patients under bDMARD treatment *versus* controls for total weight, BMI, FM and FFM showed no significant difference. The result of the mean difference for total weight in three studies with 119 patients [19, 22, 25] was 0.12 kg (95% CI − 5.58, 5.82), $p = 0.97$, $I^2 = 55\%$; and for BMI in also three studies [20, 25, 28], with 95 patients was 0.08 kg/m^2 (95% CI − 1.76, 1.92), $p = 0.93$, $I^2 = 29\%$.

In the analysis of specific BC components, the result of the mean difference for FM, carried out in two studies [19, 28], with 59 patients was − 0.08 kg (95% IC − 5.31, 5.14), $p = 0.98$, $I^2 = 0\%$; and for FFM in three studies [19, 20, 28], with 87 patients was − 2.08 kg (95% CI − 7.37, 3.21), $p = 0.44$, $I^2 = 51\%$. The Forest Plot of these results are presented as Fig. 2.

Discussion

Of the 137 studies retrieved in our search, 18 studies were included in the analyses. Ten (55.5%) studies demonstrated a significant increase in total weight and BMI after use of bDMARDs in RA patients, four of them with patients exclusively treated with anti-IL6 therapy. In total, two (11%) studies showed an increase in FM and four (22%) studies showed an increase in FFM after bDMARD use. Of interest, the studies that analyzed BC by DXA, 68.9% of the patients that increased total weight or BMI, simultaneous increased FFM, without variation on FM. These results suggest that treatment with bDMARDs in RA could improve RC. However, caution is necessary when analyzing these findings, as the meta-analysis made with five studies was not able to confirm this hypothesis, as it did not show significant difference in total weight, BMI, FM and FFM.

Hasegawa et al. [27] showed that among the 21 RA patients that fulfilled the European Working Group on Sarcopenia in Older People (EWGSOP) [31] criteria before the intervention, the number of patients having sarcopenia significantly decreased after 12 months of bDMARDs (100% vs. 52.3% $p = 0.0005$) and skeletal muscle index of these patients were significantly increased (5.1 ± 0.5 kg/m^2 vs. 5.3 ± 0.7 kg/m^2 $p = 0.046$). On the other hand, the subgroup that did not fulfill the EWGSOP criteria, did not improve the skeletal muscle index significantly. This result could explain that only the patients that lost FFM during disease activity, would benefit from the gain in FFM after bDMARD treatment. The patients that were able to maintain the FFM during disease activity, remain stable after the intervention. This information could also explain why other studies, that did not categorize the FFM in the baseline, did not show variation in body composition after bDMARD use.

Most of the studies in this systematic review evaluated the effect of TNFi and anti-IL6 on BC. Our results are in agreement with the literature data that demonstrate that the main results are related to these classes of bDMARDs.

Marouen et al. [32] demonstrated in a systematic review with meta-analysis of seven studies in RA patients compared to healthy controls that RA patients at baseline had an increased FM (+ 1.85 kg, $p = 0.02$), adiposity (+ 3.53%, $p < 0.001$) and android mass (+ 1.7 kg, $p < 0.001$) and a decrease in LM (− 3.03 kg, $p = 0.01$). After TNFi intervention, comparing baseline to six, 12 or 24 months, four studies showed an increase in FM and two in FFM.

Known as a proinflammatory cytokine, TNF impairs response to insulin in adipocytes and muscle cells, avoiding the influx of glucose and energy accumulation, besides stimulating lipolysis [33]. Previously known as cachectin, TNF has been shown to directly induce muscle loss by stimulating protein breakdown and reducing the sensitivity of skeletal muscle cells to anabolic stimuli [25]. In this way, it is expected that TNFi treatment in RA patients, may reduce muscle impairment and lipolysis and thereby increase muscle construction and fat in adipocytes [33].

The increase in FFM was found in our review among the studies that analyzed BC by DXA, although the variation in FM was not retrieved. This effect is not reported in RA patients treated with csDMARD, which suggests a specific class effect, and not only related to inflammation suppression, also in consonance with our review [32].

Binymin et al. [34] demonstrated that RA activity, presented with increased inflammatory cytokines such

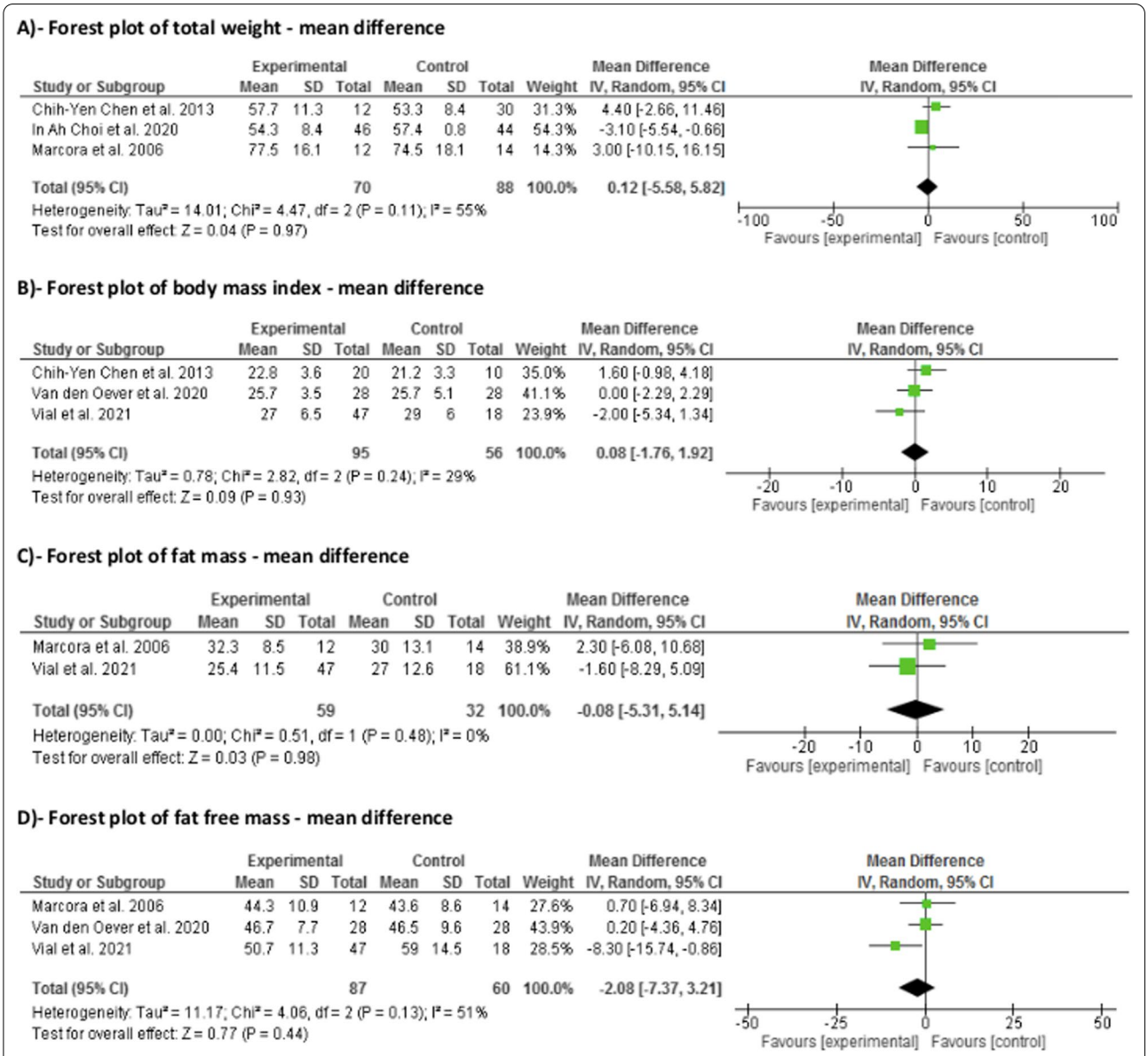

Fig. 2 Forest plot of total weight (**A**), body mass index (**B**), fat mass (**C**) and fat free mass (**D**) from meta-analysis

as TNF and IL-6, provoke RC by the increase of resting energy expenditure (REE), and not by the reduction of calorie intake. They compared RA patients in two moments, in active flare and after disease control, with matched healthy controls and observed that they had fewer FFM and increased adjusted REE. No difference in FM was observed among both groups. These studies findings demonstrated that increased RA activity leads to RC by accelerated FFM consumption determined by a combination of intensity and duration of inflammatory disease, insulin response impairs, and lipolysis. In our systematic review, 15 (83.5%) studies showed a significant decrease in DAS28, which may interfere in BC by controlling the inflammatory activity (improving insulin response, reducing of lipolysis and REE), although the gain in FFM and even in the total weight and BMI were only showed in the group of bDMARD intervention.

Challal et al. [4] quoted that RC is associated with the two major unfavorable outcomes of RA that are disability and CV mortality. Life expectancy of RA patients is reduced by 5–10 years, and underweight patients present an increased CV risk. Improvement in body composition generates a positive impact on physical function, however there is no evidence that it reduces CV risk. Many

factors are involved in the altered BC in this population, including low FFM and increased FM, and the modifiable ones, that deserve special attention are corticosteroids, low PA, poor nutrition, and inflammation. No diet intervention was proven to alter body composition; however, anti-inflammatory diet has been shown to reduce disease activity [4, 35]. High-intensity progressive resistance training has been proven to reverse RC and decrease disease activity, reinforcing the need for a multidisciplinary approach [4, 36].

In our review, DXA was the only method which was able to show a tendency of increase in FFM and its correlation with the increase in total weight and BMI; even though this finding was not confirmed by meta-analysis. This is in line with the literature data, that suggests that DXA is the gold standard method to evaluate body composition.

Conclusion

The results of this systematic review suggest a possible impact of bDMARDs on BC of RA patients, even though, the meta-analysis carried out in a small part of these studies was not able to confirm significant variation in BC components.

The review suggests that the use of DXA for BC analyzes could provide more accurate and homogeneous data in RA patients. Further studies are necessary to elucidate the effect of different DMARDs on BC components of RA patients, and the long-term impact on the disease.

Abbreviations

ACR: American College of Reumatology; Anti-CCP: Anti-cyclic citrullinated peptide; Anti-IL6: Interleukin 6 receptor inhibitor; bDMARD: Biological disease-modifying antirheumatic drugs; BMI: Body mass index; csDMARD: Conventional synthetic disease-modifying antirheumatic drugs; CV: Cardiovascular; DAS28: Disease activity score in 28 joints; Decs: *Descritores em Ciências da Saúde*; DXA: Dual X-ray absorptiometry; Emtree: Embase Subject Headings; EULAR: European Alliance of Associations for Rheumatology; FFM: Fat free mass; FM: Fat mass; JAK: Janus Kinase; MeSH: Medical Subject Headings; NOS: Escala Newcastle–Ottawa; PA: Physical activity; PRISMA: Preferred Reporting Items for Systematic Review and Meta-analysis; RA: Rheumatoid arthritis; Rayyan: Rayyan Qatar Computing Research Institute; RC: Rheumatoid cachexia; RF: Rheumatoid factor; TNFi: Tumoral necrosis factor inhibitor; tsDMARD: Targeted synthetic disease-modifying antirheumatic drugs.

Supplementary Information

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Additional file 1. Search strategy at Medical Subject Headings (MeSH), Descritores em Ciências da Saúde (Decs) and Embase Subject Headings (Emtree).

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Author contributions

MPGUSS, NSG, VAS and AMK conceived the study, developed the protocol, collected, and managed data. MPGUSS, NSG, VAS, AMK and MFBRG critically read the manuscript, corrected the text, and approved the final submitted version. We affirm that all of them actively participated and are responsible for reported research. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare conflicts of interest, autside the submitted work. MPGUSS reports personal fees from lectures for AbbVie, Amgen, Fresenius, Janssen, Novartis, Pfizer, Sandoz and UCB; AMK reports personal fees from lectures for AbbVie, Amgen, Fresenius, Eli Lilly, Janssen, Novartis, Pfizer, Sandoz and UCB; VAS reports personal fees from lectures for Abbvie, Eli Lilly, Janssen, Novartis, Pfizer, Sandoz, UCB, Roche, Astrazeneca; MFBRG reports personal fees from lectures for Ely Lily, UCB, Novartis, Janssen and Pfizer. NSG has no competing interests.

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