UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

O EFEITO DA ATIVIDADE DA DOENÇA SOBRE A CAQUEXIA EM PACIENTES COM ARTRITE REUMATOIDE: UM ESTUDO DE COORTE PROSPECTIVO

RAFAELA CAVALHEIRO DO ESPÍRITO SANTO

Porto Alegre

2018

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

O EFEITO DA ATIVIDADE DA DOENÇA SOBRE A CAQUEXIA EM PACIENTES COM ARTRITE REUMATOIDE: UM ESTUDO DE COORTE PROSPECTIVO

RAFAELA CAVALHEIRO DO ESPÍRITO SANTO

Orientador: Prof. Dr Ricardo Machado Xavier

Co-Orientador (a): Priscila Schmidt Lora

Tese apresentada como requisito parcial para obtenção do título de Doutora em Medicina: Ciências Médicas, da Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Medicina: Ciências Médicas.

Porto Alegre

2018

CIP - Catalogação na Publicação

Cavalheiro do Espirito Santo, Rafaela
O efeito da atividade da doença sobre a caquexia em pacientes com artrite reumatoide: Um estudo de coorte prospectivo / Rafaela Cavalheiro do Espirito Santo. -- 2018.
114 f.
Orientador: Ricardo Machado Xavier.

Coorientador: Priscila Schmidt Lora.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Medicina: Ciências Médicas, Porto Alegre, BR-RS, 2018.

1. Artrite reumatoide. 2. Caquexia reumatoide. 3. Caquexia . 4. Composição corporal. 5. Função Física. I. Machado Xavier, Ricardo, orient. II. Schmidt Lora, Priscila, coorient. III. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

No que diz respeito ao empenho, ao compromisso, ao esforço, à dedicação, não existe meio termo. Ou você faz uma coisa bem-feita ou não faz.

Ayrton Senna

AGRADECIMENTOS

Agradeço e dedico este trabalho as primeiras pessoas que me ensinaram o que é amor pela família, independentemente de qualquer problema ou dificuldade, Delce Cavalheiro e Fifi Bessestil Cavalheiro (*in memoriam*). Também agradeço e dedico a quem esteve sempre ao meu lado, me apoiando em todos os momentos e que sempre torceu e torcerá por mim: minha mãe Ionara Cavalheiro. Não menos importante, agradeço à minha família, por serem a base da minha vida, pelo apoio, dedicação e amor incondicional.

Agradeço ao Prof. Dr. Ricardo Machado Xavier, meu orientador, por ter me aceito e orientado neste trabalho, por sua compreensão e exemplo científico.

À Prof. Priscila Lora, que propôs estudar o assunto, por sua compreensão, exemplo científico e por sempre me incentivar a buscar o melhor.

Aos colegas e amigos do Laboratório de Doenças Autoimunes, em especial Jordana Souza, Mirian Farinon e Eduarda Freitas, minhas fiéis escudeiras, que estiveram comigo deste o mestrado até o presente momento.

Agradeço minhas amigas e amigos, em especial à Alessandra Haupt do Couto, que sempre estive ao meu lado, me aguentando, me incentivando, vibrando com as minhas pequenas vitórias e me ajudando a levantar nos momentos difíceis.

À Universidade Federal do Rio Grande do Sul.

Ao Hospital de Clínicas de Porto Alegre.

Ao Serviço de Reumatologia do Hospital de Clínicas de Porto Alegre.

À Fundação de Incentivo a Pesquisa (FIPE) do Hospital de Clínicas de Porto Alegre.

À Coordenação de Aperfeiçoamento de Pessoas de Nível Superior (CAPES), pelo apoio financeiro.

RESUMO

Base teórica: A artrite reumatoide (AR) é uma doença autoimune, que envolve inflamação crônica, comprometimento articular e extra-articular. Entre as manifestações extra-articulares estão às alterações de composição corporal. A diminuição da massa livre de gordura e o aumento da massa gorda em pacientes com AR são denominados caquexia reumatoide (CR), enquanto caquexia clássica é determinada pela perda de peso corporal de 5% ou mais em 12 meses, além de outras características. Na AR, há poucos dados avaliando a prevalência e progressão da caquexia ao longo do tempo, bem como seus fatores associados. **Objetivos:** Avaliar a prevalência de caquexia reumatoide e fatores associados a esta condição em uma coorte de pacientes com artrite reumatoide. **Métodos:** Pacientes com AR, segundo os critérios de classificação do ACR/EULAR 2010, foram recrutados de forma consecutiva em uma clínica de AR de um hospital universitária e acompanhada inicialmente por doze meses. As seguintes avaliações foram realizadas no início e após um ano: estado da doença (atividade da doença pelo DAS28 e drogas), composição corporal por densitometria por dupla emissão de raios-X, função física (HAQ-DI, força de preensão palmar pelo dinamômetro Jamar, velocidade da marcha pelo teste Timed Up and Go (TUG) e a força dos membros inferiores pelo teste sentar e levantar da cadeira por 30 segundos), fadiga pela escala The Functional Assessment of Chronic Illness Therapy fatigue, anorexia pela escala The Functional Assessment of Anorexia/Cachexia Therapy, marcadores inflamatórios e bioquímicos séricos. Para diagnosticar caquexia foram utilizados três critérios de diagnóstico, sendo os dois primeiros específicos para a caquexia reumatoide e o terceiro para caquexia clássica. Engvall e colaboradores propuseram caquexia reumatoide quando pacientes com AR apresentassem: índice de massa livre de gordura (IMLG) abaixo do percentil 10 e índice de massa gorda (IMG) acima do percentil 25. Elkan e colaboradores propuseram caquexia reumatoide quando pacientes com AR apresentassem: IMLG abaixo do percentil 25 e IMG acima do percentil 50. Evans e colaboradores propuseram caquexia clássica quando pacientes apresentassem: perda de peso de 5% ou mais dentro de 12 meses (ou índice de massa corpórea (IMC)≤20 kg/m2) e pelo menos três dos seguintes fatores:

diminuição da força muscular; fadiga; anorexia; baixo IMLG; bioquímica anormal (aumento dos marcadores inflamatórios [Proteína C Reativa(PCR),interleucina (IL)-6], anemia [Hemoglobina(Hb)<12g/dL], albumina baixa no soro [<3,2g/dL]. A análise de frequência, teste t-Student pareado, o teste de McNemar e as análises por Modelo de Equações de Estimações Generalizadas (GEE) foram utilizados e a significância estatística foi considerada como p<0,05. A análise dos dados foi realizada no software SPSS 21.0. **Resultados:** Dos 90 pacientes incluídos, 81 pacientes com AR completaram o estudo. A maioria dos pacientes eram do sexo feminino (88,9%), com idade de 56,5±7,3 anos, com atividade moderada da doença (média do DAS28 (Disease Activity Score 28) 4,0±1,3). Caquexia reumatoide foi encontrada em 13,3% dos pacientes com AR utilizando os critérios de Engvall e colaboradores e 30% usando os critérios de Elkan e colaboradores no início do estudo. Usando critério diagnóstico para caquexia clássica proposta por Evans e colaboradores, não encontramos caquexia em nossos pacientes. Quanto à função física, a força de preensão manual foi o parâmetro que apresentou diminuição estatisticamente significativa após 12 meses (p<0,05). Remissão de doença foi significativamente associada com as alterações no IMLG, IMG, HAQ, força de preensão manual e força dos membros inferiores (p<0,05) em relação a pacientes com doença em atividade ao longo dos 12 meses. O tratamento com DMCDs biológicos associou-se significativamente com alterações no IMLG, velocidade da marcha e força muscular de membros inferiores ao longo dos 12 meses (p<0,05). **Conclusão:** Caquexia reumatoide foi frequente quando utilizados os critérios específicos, mas nenhum paciente apresentou os critérios de caquexia clássica. Além disto, a função física é um parâmetro que merece destaque, pois ela apresentou-se prejudicada desde o início do estudo e se manteve após um ano de acompanhamento. As observações de que o estado de remissão está associado às alterações da função física e da composição corporal ao longo do tempo enfatizam a importância do controle adequado da atividade da doença. As observações sobre o efeito do tratamento biológico na caquexia foram controversas, demonstrando a necessidade de mais estudos avaliando estes parâmetros. **Palavras chave:** Artrite Reumatoide; Caquexia; Caquexia Reumatoide; Composição Corporal; Função Física.

ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune disease, which involves chronic inflammation, joint and extra-articular involvement. Among the extra-articular manifestations are the changes in body composition. The decrease in fat-free mass and the increase in fat mass in RA patients are termed rheumatoid cachexia (CR), while classic cachexia is determined by 5% or more body weight loss over 12 months, as well as other characteristics. In RA, there is little data evaluating the prevalence and progression of cachexia over time, as well as its associated factors. **Objectives**: To evaluate the prevalence of rheumatic cachexia and factors associated with this condition in a cohort of patients with rheumatoid arthritis. **Methods:** RA patiens, according to the classification criteria of ACR/EULAR 2010, were recruited consecutively in a RA clinic of a university hospital and initially followed up for twelve months. The following evaluations were performed at baseline and after one year: disease status (disease activity by DAS28 and drugs), body composition by X-ray dual-density densitometry, physical function (HAQ-DI, palmar grip strength by dynamometer Jamar, gait velocity by the Timed Up and Go (TUG) test and the strength of the lower limbs by the sit and stand test for 30 seconds), fatigue by the scale The Functional Assessment of Chronic Illness Therapy fatigue, anorexia by The Functional Assessment of Anorexia/Cachexia Therapy, inflammatory markers and serum biochemists. Three diagnostic criteria were used to diagnose cachexia, the first two being specific for rheumatoid cachexia and the third for classical cachexia. Engvall et al proposed rheumatoid cachexia when patients with RA presented: fat free mass index (FFMI) below the 10th percentile and fat mass index (FMI) above the 25th percentile. Elkan et al proposed rheumatoid cachexia when RA patients presented: FFMI below the 25th percentile and FMI above the 50th percentile. Evans et al proposed classic cachexia when patients presented: weight loss of 5% or more within 12 months (or body mass index (BMI)≤20 kg/m^2) and at least three of the following factors: decreased muscle strength; fatigue; anorexia; low FFMI; (C-reactive protein (CRP), interleukin (IL)-6], anemia [hemoglobin (Hb)<12g/dL], serum albumin [<3,2g/dL]. (Student's t-test, McNemar's test, and Generalized Estimating Equation (GEE) model analyzes were used and the statistical significance was considered as $p<0.05$. Data analysis was performed in SPSS 21.0 software.

Results: Of the 90 patients included, 81 RA patients completed the study. The majority of the patients were female (88.9%), aged 56.5±7.3 years, with moderate disease activity (DAS28 (Disease Activity Score 28) 4.0±1.3). Rheumatoid cachexia was found in 13.3% of RA patients using the criteria of Engvall et al. and 30% using the criteria of Elkan et al. at baseline. Using diagnostic criteria for classical cachexia proposed by Evans et al. We did not find cachexia in our patients. Regarding physical function, manual grip strength was the parameter that showed a statistically significant decrease after 12 months ($p<0.05$). Disease remission was significantly associated with changes in FFMI, FMI, HAQ, manual grip strength and lower limb strength ($p<0.05$) relative to patients with active disease over 12 months. Treatment with biological DMARDs was significantly associated with changes in FFMI, gait velocity, and lower limb muscle strength over the 12 months ($p<0.05$). **Conclusion:** Rheumatoid cachexia was frequent when specific criteria were used, but no patient presented classic cachexia criteria. In addition, physical function is a parameter that deserves to be highlighted, since it has been impaired since the beginning of the study and was maintained after one year of follow-up. Observations that remission status is associated with changes in physical function and body composition over time emphasize the importance of adequate control of disease activity. Observations on the effect of biological treatment on cachexia were controversial, demonstrating the need for further studies evaluating these parameters. **Keywords:** Rheumatoid Arthritis; Cachexia; Rheumatoid Cachexia; Body Composition; Physical Function.

LISTA DE FIGURAS DA REVISÃO DA LITERATURA

LISTA DE TABELAS DA REVISÃO DA LITERATURA

LISTA DE ABREVIATURAS E SIGLAS DA REVISÃO DA LITERATURA

AAPC	Anticorpos antiproteína/peptídeo citrulinados
ACR	Colégio Americano de Reumatologia *(American College of Rheumatology)*
anti-PC	Lipídios e anticorpos naturais ateroprotectores contra a fosforilcolina
APCs	Células apresentadoras de antígenos (*antigen-presenting cells)*
AR	Artrite reumatoide (*Rheumatoid Arthrits*)
BCM	Massa celular corporal (*Body Cell Mass*)
BIA	Impedância bioelétrica
CR	Caquexia reumatoide (*Rheumatoid Cachexia*)
CDAI	Índice clínico de atividade da doença (*Clinical Disease Activity Index)*
CMTC	Carpometacarpiana
CR	Caquexia reumatoide
Cr	Creatina
DAS28	Escore de Atividade da Doença (*Disease Activity Score 28*)
DCV	Doenças cardiovasculares
DEXA	Densitometria por dupla emissão de raios-X
DMCD	Drogas modificadoras do curso da doença
EVA	Escala visual analógica
FAACT	*Functional Assessment of Anorexia/Cachexia Therapy*
FACIT-F	*Functional Assessment of Chronic Illness Therapy-Fatigue*
FLS	Fibroblastos
FR	Fator Reumatoide (*Rheumatoid fator*)
GEE	Modelo de Equações de Estimações Generalizadas (*Generalized Estimating Equations Analysis*)
GER	Gasto energético de repouso
HAQ-DI	Questionário de Avaliação da Saúde e Índice de Incapacidade *(Health Assessment Questionnaire Disability Index)*
Hb	Hemoglobina
HCPA	Hospital de Clínicas de Porto Alegre
HDL	Lipoproteína de alta densidade

HMB/GL N/ARG	Mistura de b-hidroxi-b-metilbutirato, glutamina e arginina
IC	Intervalo de confiança (*confidence interval*)
IFDs	Articulações interfalangeanas distais
IFN-γ	Interferon gama
IGF-1	Fator de crescimento semelhante à insulina tipo 1
IL	Interleucina (*Interleukin)*
IMC	Índice de massa corpórea
IMG	Índice de massa gorda
IMGL	Índice de massa livre de gordura
IMMA	Índice de massa magra apendicular (*Apendicular lean mass index)*
LDL	Lipoproteína de baixa densidade
LSN	Limite superior normal
MA	Medidas antropométricas
MeSH	Termos para buscas (*Medical Subject Headings*)
MG	Massa gorda
MHC	Complexo principal de histocompatibilidade
MLG	Massa livre de gordura
MMPS	Metaloproteinases da matriz (*matrix metalloproteínases*)
MCF	Metatarsofalangeana
NF- Kb	Fator nuclear kappa B (*factor nuclear kappa B*)
PCR	Proteína C Reativa (Protein C Reativa)
RANKL	Ligante do receptor ativador do fator nuclear κb
SDAI	Índice de atividade da doença simplificada (*Simple Disease Activity Index)*
TBK	Contagem de potássio total no corpo (*Total body potassium*)
TCR	Receptor de células T (T cell receptor)
TCZ	Tocilizumabe (*Tociluzimab*)
TGF-1β	Fator de crescimento transformador beta
TLR	Receptor do tipo Toll 4 (*Toll-like receptor)*
TNF-α	Fator de necrose tumoral alfa (*Tumor necrosis fator*)
TUG	*Timed Up and Go test*
VSG	Velocidade de sedimentação globular

SUMÁRIO

1. INTRODUÇÃO

A artrite reumatoide (AR) é uma doença autoimune, inflamatória e crônica (1,2). Como característica principal, a AR apresenta poliartrite crônica simétrica de grandes e pequenas articulações. Sua prevalência é de 0,5-1% da população adulta mundial (1,3,4) e 0,2-1% na população brasileira (5). A incidência desta doença aumenta com a idade com pico na quinta década de vida, sendo três vezes mais frequente em mulheres (6).

O aumento de citocinas pró-inflamatórias, especialmente o fator de necrose tumoral alfa (TNF-α) e interleucinas (IL) -1β, IL-6 e IL-17 estão envolvidas no processo de inflamação articular, que culmina na degradação da cartilagem e na erosão óssea. Contudo, estas moléculas atuam sistemicamente e provocam aumento do metabolismo e catabolismo proteico, resultando em alterações de composição corporal (7–9).

Manifestações extra-articulares como redução da massa livre de gordura (MLG), cuja massa muscular é o principal componente, associada ao aumento da massa gorda (MG), com pouca ou nenhuma perda de peso e de índice de massa corporal (IMC), são observadas em pacientes com AR (7,10–13). Atualmente, este conjunto de alterações de composição corporal é descrito como caquexia reumatoide (CR) (7,10–13).

São diversos os critérios de diagnóstico para CR descritos pela literatura, e isso impacta em diferentes taxas de prevalência. Engvall e colaboradores (14) foram os primeiros autores a propor um critério de diagnóstico. Este critério é determinado por índice de MLG (IMLG) abaixo do percentil 10 com índice de MG (IMG) acima do percentil 25. Em seguida, Elkan e colaboradores (15) propuseram um ajuste nos pontos de corte deste mesmo critério (14), IMLG abaixo do percentil 25 com IMG acima do percentil 50. Em outra perspectiva, Evans e colaboradores (16) propuseram critério de diagnóstico de caquexia para várias doenças, incluindo AR, no qual o diagnóstico de caquexia é determinado pela perda de peso de 5% ou mais dentro de 12 meses (ou IMC ≤20 kg/m^2) e pelo menos três dos seguintes fatores: diminuição da força muscular; fadiga; anorexia; baixo IMLG; bioquímica anormal (aumento dos marcadores inflamatórios [PCR, IL-6], anemia [Hb<12 g/dL], albumina baixa no soro [<3,2 g/dL]. Os três critérios estão descritos na tabela 1.

Tabela 1- Critérios de diagnóstico de caquexia clássica e CR encontrados na literatura.

Autores	Peso corporal	IMLG	IMG	Outros
Engvall e colaboradores (14)	-	<percentil 10	>percentil 25	-
Elkan e colaboradores (15)	-	<percentil 25	>percentil 50	-
Evans e colaboradores (16)	Perda de peso de 5% ou mais dentro de 12 meses (ou um IMC ≤20 kg/m^2).	<5.45 kg/m^2 para mulheres; <7.25 kg/m^2 para homens.	-	Força muscular reduzida; Fadiga; Anorexia; Bioquímica anormal.

Considerando que os critérios de diagnóstico de CR na literatura são heterogêneos, a prevalência de CR também é heterogênea. De acordo com a revisão sistemática com metanálise publicada por nosso grupo (**primeiro artigo desta tese**), a prevalência estimada de CR varia entre 15% e 32% e é influenciada pelo método de avaliação da composição corporal e critério de diagnóstico escolhido (17). Uma vez que os critérios não são padronizados e a prevalência é discutível, a associação com desfechos clínicos fica limitada.

Assim, três perguntas necessitam ser investigadas: qual a prevalência estimada de CR? Esta prevalência é variável conforme os diferentes critérios existentes na literatura? Quais são os fatores associados à CR em pacientes com AR e como evoluem ao longo tempo? Portanto, a tese segue a disposição de: uma revisão da literatura, seguida de dois artigos escritos durante o processo de doutoramento, os quais respondem as três perguntas norteadoras desta tese.

2. REVISÃO DA LITERATURA

Nessa sessão será apresentado o referencial teórico que fundamentou este estudo.

2.1. ESTRATÉGIAS PARA LOCALIZAR E SELECIONAR AS INFORMAÇÕES

Esta revisão de literatura está focada em sumarizar as informações relacionadas à CR em pacientes com AR. A estratégia de busca envolveu as seguintes bases de dados: PubMed, Lilacs e Embase. As buscas foram realizadas utilizando descritores (MeSH): “Rheumatoid Arthritis”, “body composition”, “diagnostic criteria”, e a palavra-chave “rheumatoid cachexia” cruzados entre si, adaptados para cada base. Foram lidos os resumos dos artigos encontrados, com posterior seleção baseada nos seguintes critérios de inclusão: caquexia, artrite reumatoide, prevalência de caquexia reumatoide, composição corporal e função física. Foram considerados como critério de exclusão estudos que não envolviam seres humanos. Os resultados da pesquisa estão apresentados na Figura 1.

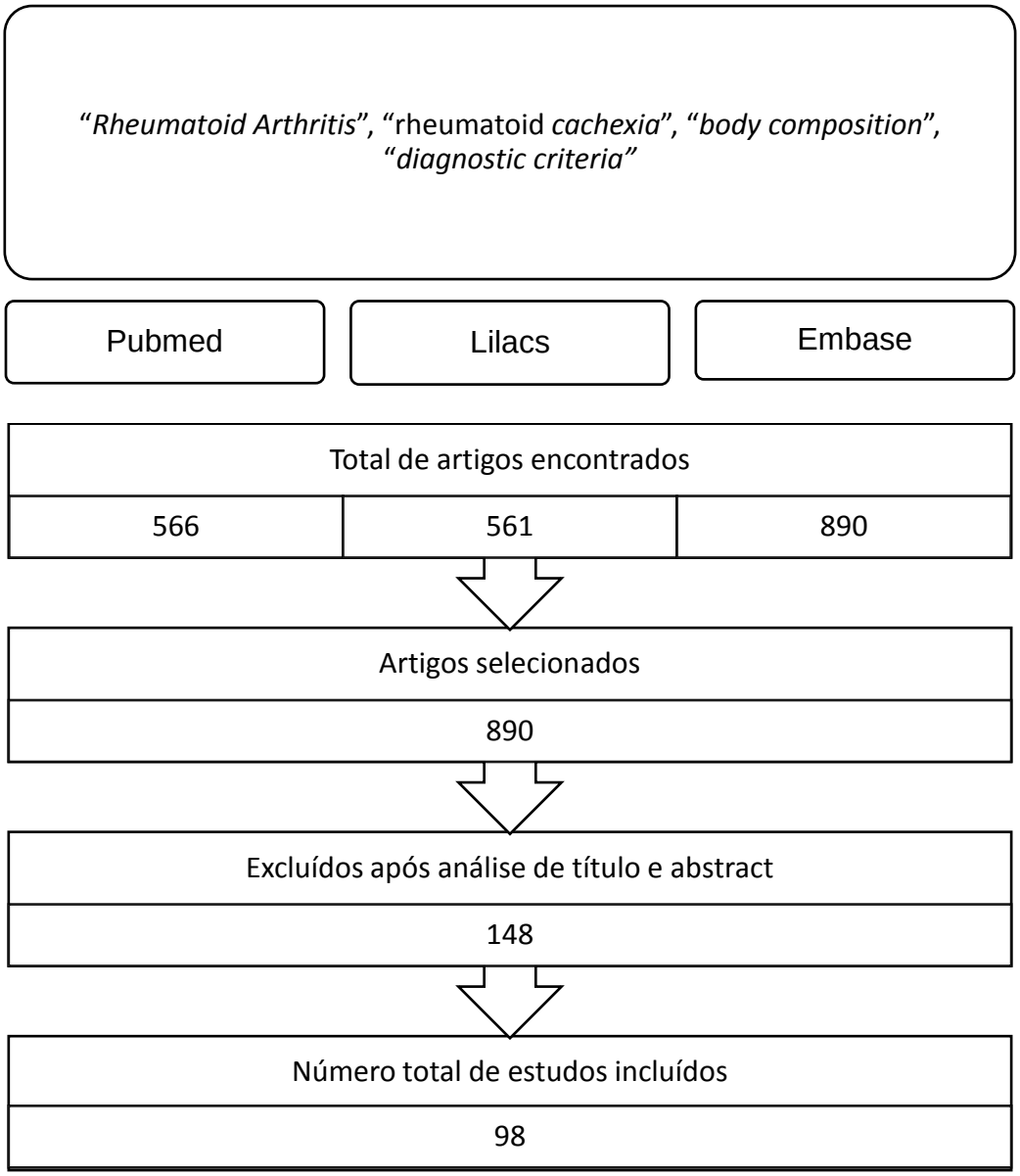


Figura 1. Estratégias de busca de referências bibliográficas, através das bases de dados que fundamentam os objetivos desta tese.

2.2. ARTRITE REUMATOIDE

A AR é uma doença autoimune, inflamatória e crônica (1,2), tendo como característica principal poliartrite crônica simétrica de grandes e pequenas articulações (18). Devido a sua cronicidade, a doença constitui um importante problema de saúde pública, gerando altos custos de tratamento, bem como um importante fator sociocultural. Estas questões justificam os esforços na elucidação de sua patogênese, diagnóstico e tratamento (19,20). A prevalência é de 0,5-1% da população adulta mundial (1,3,4) e 0,2-1% da população brasileira (5). A AR é três vezes mais frequente em mulheres e sua incidência aumenta com a idade, atingindo um pico na quinta década de vida (6).

Apesar da etiologia da AR não ser completamente descrita, sabe-se que ela resulta de uma complexa interação entre mutações genéticas, fatores ambientais e quebra da tolerância imunológica. O evento característico resultante deste processo é a inflamação sinovial com padrão simétrico (1,2).

No processo inflamatório da membrana sinovial, os neutrófilos contribuem através da síntese de mediadores inflamatórios que propagam o sinal como prostaglandinas, quimiocinas e citocinas. Além disto, através da liberação do conteúdo dos grânulos como proteases e espécies reativas de oxigênio e nitrogênio, após sua ação de fagocitose o que leva a destruição tecidual. Citocinas são proteínas associadas às células produzidas por células inflamatórias que funcionam como mediadores intercelulares parácrinos. Além dos neutrófilos, outras células também auxiliam na propagação deste processo como macrófagos, que liberam TNF-α, IL-1β, IL-6, espécies reativas de oxigênio e nitrogênio e metaloproteinases da matriz (MMPs), além de realizarem fagocitose e apresentação de antígenos (1,3,21). Isto resulta em proliferação de linfócitos T (principalmente CD4+) e B, estimulação da proliferação de vasos sanguíneos na membrana sinovial, acúmulo de células inflamatórias, incluindo leucócitos polimorfonucleares, proliferação de células sinoviais e desenvolvimento de *pannus* (3,21,22). Linfócitos B são precursoras de plasmócitos secretores de autoanticorpos, processam e apresentam antígenos promovendo a ativação de linfócitos T e secretam citocinas pro-inflamatórias, como IL-6 e TNF-α.

As células T CD4+ que produzem IL-2 e interferon (IFN)-γ apresentam uma polaridade de resposta T helper (Th1) (22). Embora a AR seja considerada

uma doença mediada por células Th1, o papel das células Th17 no processo de destruição articular vem ganhando importância. Essas células produzem IL-17 e TNF-α que, sinergicamente, promovem a ativação de fibroblastos (FLS) sinoviais e inibe condrócitos (21,22).

Os FLS sinoviais de pacientes com AR assumem um fenótipo agressivo e tumoral, com inibição por contato diminuída, resistência à apoptose e migração aumentada. Essas células secretam MMPs, moléculas de adesão e o ligante do receptor ativador do fator nuclear κB (RANKL), que promove a diferenciação de osteoclastos, os quais promovem reabsorção óssea e dano ao osso subjacente à cartilagem articular (23).

Adicionalmente à inflamação e dano articular, ocorre o dano à cartilagem e ao osso subjacente à cartilagem articular. O dano da cartilagem ocorre através da secreção de MMPs por macrófagos e FLS constituintes do *pannus*, que desorganiza a rede de colágeno do tipo II e altera o conteúdo de glicosaminoglicanos e à retenção de água, levando a degeneração do tecido. Ainda, o potencial de regeneração do tecido está limitado, uma vez que citocinas presentes no ambiente articular doente, principalmente IL-1 e IL-17, e espécies reativas de nitrogênio promovem a apoptose dos condrócitos, tipo celular que regula a formação e clivagem da matriz cartilaginosa (3,21,24). O dano ao tecido ósseo é mediado pelos osteoclastos, que tem sua diferenciação ativada por fatores como RANKL, TNF-α, IL-1, IL-6 e IL-17 (1,25).

As citocinas produzidas nas articulações de pacientes com AR também são produzidas no músculo esquelético, gordura e outros tecidos (24), levando a diversas alterações extra-articulares. Pacientes com AR possuem um risco aumentado de desenvolver manifestações extra-articulares e comorbidades (26), como doenças cardiovasculares (27,28), linfoma (29), doença pulmonar (30,31), osteoporose (32,33), entre outras (26). Essas manifestações agravam o quadro da doença, levando à incapacidade funcional e diminuição na qualidade de vida dos pacientes, além do aumento da mortalidade (34–36).

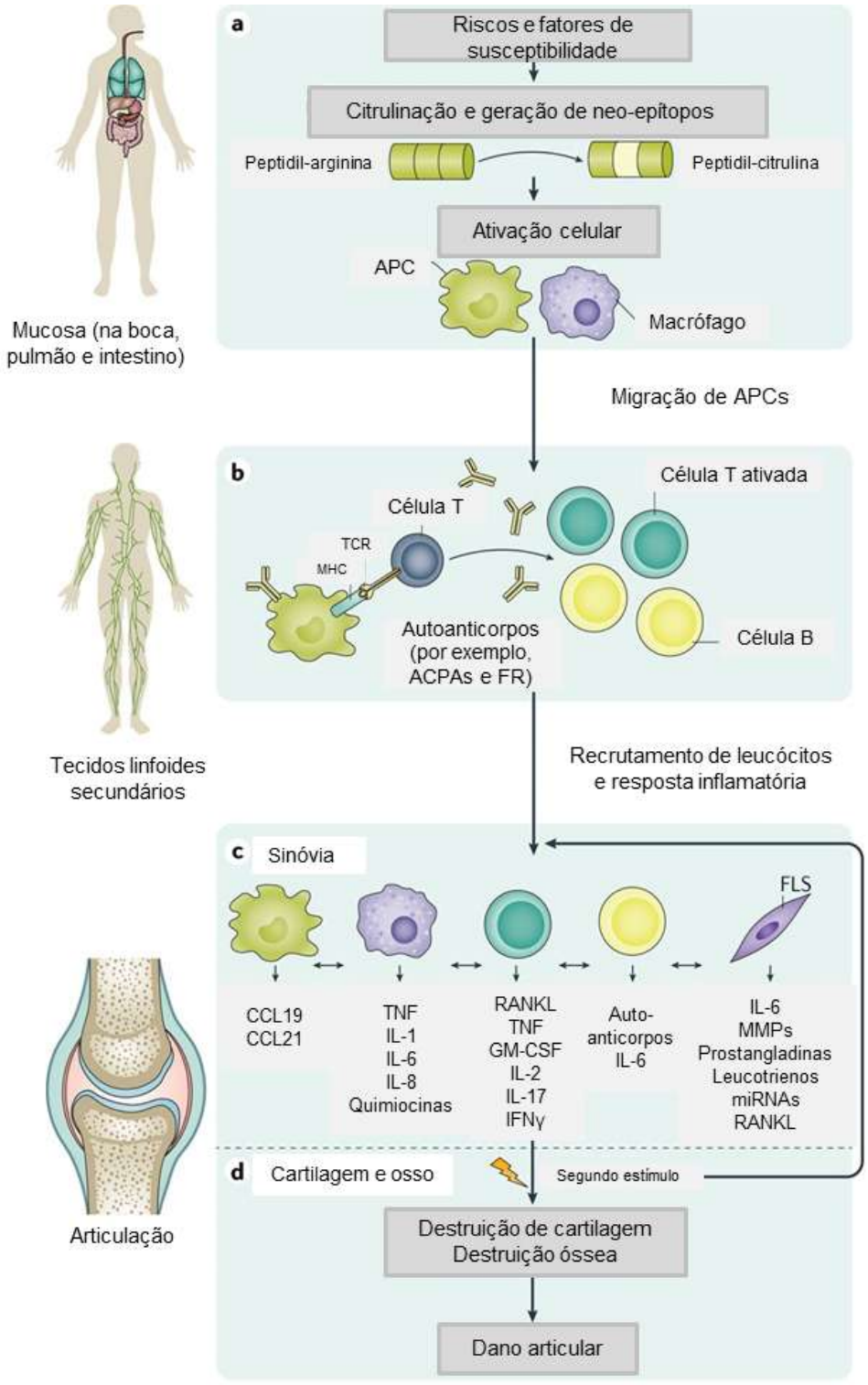


Figura 2. Mecanismos que envolvem o início e a progressão da AR. **a)** Modificações pós-traducionais, tais como citrulinação ou carbamilação, na mucosa pode criar neo-epitopos que podem ser reconhecidos pelo sistema imune adaptativo. **b)** Estes peptídeos alterados são apresentados por células apresentadoras de antígenos (APCs), ativam uma resposta imune adaptativa em tecidos linfoides e elicitar a formação de autoanticorpos. **c)** Células estromais (como sinoviócitos tipo fibroblastos (FLS)), APCs e macrófagos podem ser ativados localmente e produzir uma série de citocinas pró-inflamatórias. A resposta autoimune provocada pelo sistema imunológico desencadeia inflamação sinovial, mas pode exigir um segundo ataque, como formação de complexos imunes e ativação do complemento, para induzir ou aumentar a produção de citocinas e vazamento vascular sinovial. **d)** Parácrina e ações autócrinas de

citocinas, juntamente com respostas imunes adaptativas persistentes, pode perpetuar a doença e, finalmente, levar à destruição da cartilagem e do osso. APCs, células apresentadoras de antígeno; CCL19, ligante de quimioquina CC 19; CCL21, ligante de quimioquina CC 21; GM-CSF, fator estimulador de colônias de granulócitos-macrófagos; complexo principal de histocompatibilidade (MHC),miRNA, microRNA; MMP, matriz metaloproteinase; RANKL, ativador do receptor do ligante do fator nuclear-kB; FR,Fator reumatóide; TCR, receptor de células T; TNF, fator de necrose tumoral. **Fonte:** Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P,Firestein G. Rheumatoid arthritis. Nat Rev Dis Primers. 2018

2.3. DIAGNÓSTICO E MONITORAMENTO DA ARTRITE REUMATOIDE

O diagnóstico da AR é usualmente baseado em critérios de classificação (tabela 1) estabelecidos pelo Colégio Americano de Reumatologia *(ACR, American College of Rheumatology*) e a última modificação foi realizada por Aletaha e colaboradores (37). Para o monitoramento da atividade da doença foi proposto em 1990 um índice de medida de atividade da AR chamado Escore de Atividade da Doença (*DAS*, *Disease Activity Score)* (38).

O DAS 28 é o índice mais utilizado na prática clínica, avaliando 28 articulações (ombros, cotovelos, punhos, metacarpofalangeanas, interfalangeanas proximais e joelhos), e avaliação global do paciente por escala visual de 0 a 100. Existem dois marcadores inflamatórios utilizados na equação do DAS28 que são proteína C reativa (PCR) ou velocidade de hemossedimentação (VHS). A partir destas informações, faz-se um cálculo que resulta em um escore, o qual é interpretado como: remissão (DAS≤2,6), baixa atividade da doença (2,6>DAS≤3,2), moderada atividade da doença (3,2>DAS≤5,1), e alta atividade da doença (DAS>5,1) (39).

Como o cálculo do DAS28 é complexo e requer um instrumento tecnológico para seu cálculo, foram propostos índices mais simples como o índice de atividade da doença simplificada (*SDAI, Simple Disease Activity Index)* (40) e o índice clínico de atividade da doença (CDAI, *Clinical Disease Activity Index*). O SDAI é calculado através da soma simples do número de articulações edemaciadas e dolorosas, as mesmas avaliadas no DAS28, da avaliação da atividade da doença feita pelo paciente numa escala visual analógica de 0 a 10 cm, da avaliação da atividade da doença feita pelo médico (0-10 cm) e da PCR (mg/dL)(40). O CDAI é o instrumento mais simples do que o SDAI e DAS28. Este é calculado através da soma das articulações edemaciadas e dolorosas, as mesmas avaliadas no DAS28 e SDAI, avaliação da atividade da doença feita pelo paciente numa escala visual analógica de 0 a 10 cm, da avaliação da

atividade da doença feita pelo médico (0-10 cm); entretanto, não se incluí os marcadores inflamatórios PCR e VSG(41–43).

O monitoramento da AR também inclui a avaliação de classificação funcional do paciente. Steinbrocker e colaboradores (44) sugeriram a criação do índice funcional, em que a doença é classificada de I a IV. Entretanto, Hochberg e colaboradores (45) realizaram uma revisão dos critérios de classificação funcional (tabela 3) sendo atualmente a mais utilizada.

Para avaliação da funcionalidade do paciente é utilizado o questionário autorrelatado de capacidade funcional chamado questionário de avaliação de saúde (*HAQ-DI, Health Assessment Questionnaire disability index*)(46). Trata-se de um questionário com 20 perguntas sobre a vida cotidiana do paciente, no qual avaliam-se oito áreas de atividades funcionais habituais. Seu escore é calculado através da média aritmética do maior escore de cada uma das oito áreas avaliadas e o resultado final varia de 0 a 3, onde 0 indica nenhum prejuízo da função física e 3 completa incapacidade física (46).

Tabela 2 – Critérios classificatórios para diagnóstico de AR modificado a partir de Aletaha et al (37).

Envolvimento articular [a]	0-5
1 grande articulação [b]	0
2-10 grandes articulações	1
1-3 pequenas [c] articulações (com ou sem envolvimento de grandes articulações)	2
4-10 pequenas articulações (com ou sem envolvimento de grandes articulações)	3
>10 articulações [d] (pelo menos uma pequena articulação)	5
Sorologia [e] ***(pelo menos o resultado de um teste é necessário para classificação)***	0-3
FR negativo e AAPC negativo	0
FR positivo em título baixo ou AAPC positivo em título baixo	2
FR positivo em título alto ou AAPC positivo em título alto	3
Provas de fase aguda [f] ***(pelo menos o resultado de um teste é necessário para classificação)***	0-1
PCR normal e VHS normal	0
PCR anormal ou VHS anormal	1
Duração dos sintomas [g]	0-1
< 6 semanas	0
≥ 6 semanas	1

[a] O envolvimento articular se refere a qualquer articulação edemaciada ou dolorosa ao exame físico e pode ser confirmado por evidências de sinovite detectada por um método de imagem. As articulações interfalangeanas distais (IFDs), primeira carpometacarpiana (CMC) e primeira metatarsofalangeana (MTF) são excluídos da avaliação. As diferentes categorias de acometimento articular são definidas de acordo com a localização e o número de articulações envolvidas (padrão ou distribuição do acometimento articular). A pontuação ou colocação na

categoria mais alta possível é baseada no padrão de envolvimento articular.[b] São consideradas grandes articulações: ombros, cotovelos, quadris, joelhos e tornozelos. [c] São consideradas pequenas articulações: punhos, MCF, IFP, interfalangeana do primeiro quirodáctilo e articulações MTF. [d] Nesta categoria, pelo menos uma das articulações envolvidas deve ser uma pequena articulação; as outras articulações podem incluir qualquer combinação de grandes e pequenas articulações, bem como outras não especificamente mencionadas em outros lugares (por exemplo, temperomandibular, acromioclavicular e esternoclavicular). [e] Negativo refere-se a valores (Unidade Internacional-UI) menores ou iguais ao limite superior normal (LSN) para o método e laboratório. Título positivo baixo corresponde aos valores (UI) maiores que o LSN, mas menores ou iguais a três vezes o LSN para o método e laboratório. Título positivo alto: valores maiores que 3 vezes o LSN para o método e laboratório. Quando o FR só estiver disponível como positivo ou negativo, um resultado positivo deve ser marcado como "positivo em título baixo". [f] Normal / anormal é determinado por padrões laboratoriais locais (*Outras causas de elevação das provas de fase aguda devem ser excluídas*). [g] Duração dos sintomas se refere ao relato do paciente quanto a duração dos sintomas ou sinais de sinovite (por exemplo, dor e inchaço) nas articulações que estão clinicamente envolvidas no momento da avaliação, independentemente do status do tratamento. FR = fator reumatoide; AAPC = anticorpos antiproteína/peptídeo citrulinados; LSN = limite superior do normal; VHS = velocidade de hemossedimentação; PCR = proteína C-reativa.

Tabela 3 – Critérios de classificação funcional da AR conforme Hochberg e colaboradores(45)

Classe I	Completamente capaz de desempenhar atividades usuais da vida diária;
Classe II	Capaz de realizar atividades usuais de cuidados pessoais e vocacionais (trabalho, escola), porém, limitado nas atividades recreativas;
Classe III	Capaz de realizar atividades usuais de cuidados pessoais, porém limitado nas atividades vocacionais e recreativas;
Classe IV	Limitado na habilidade de realizar atividades usuais de cuidados pessoais vocacionais e recreativas

2.4. CAQUEXIA REUMATOIDE

Pacientes com AR, como citado anteriormente, apresentam aumento de citocinas pró-inflamatórias que conduzem a inflamação e o processo destrutivo progressivo (1,21). A produção de citocinas pró-inflamatórias na AR está associada a um metabolismo alterado, resultando em alterações na composição corporal dos pacientes (7,9). Este é caracterizado pela redução da MLG, cuja massa muscular é o principal componente, associada ao aumento da MG com pouca ou nenhuma perda de peso e IMC (7,10–13). Este conjunto de alterações de composição corporal é descrito atualmente como caquexia reumatoide (CR) (7,10–13).

Em 1893, James Paget descreve que pacientes com AR têm perda muscular não associada ao desuso (47), denominando este quadro como CR. Mais adiante, Roubenoff e colaboradores definiram CR como a condição de redução de massa celular corporal (BCM, do inglês Body Cell Mass)(8). Além

da diminuição da massa celular corporal relacionada ao hipermetabolismo induzido pelas citocinas pró-inflamatórias da AR(9), estudos demonstraram que o gasto energético de repouso (GER) está aumentado na CR (9,13), definindo assim CR como uma condição no qual os pacientes apresentam diminuição da massa celular corporal com o aumento do gasto energético de repouso (9,13).

Outros estudos ampliaram a definição de CR para síndrome complexa caracterizada por alterações hormonais, metabólicas e comportamentais que influenciam na diminuição da massa magra, com manutenção ou leve elevação da massa gorda (total de tecido adiposo), resultando em limitada ou nenhuma perda de peso (massa total) (9,48,49), o que é observado em aproximadamente dois terços de pacientes com AR (13).

Sabe-se que os mecanismos da CR são processos complexos (13,50). Na AR, o excesso de citocinas pró-inflamatórias é considerado o mecanismo principal da CR (9). Na tabela abaixo serão apresentados os efeitos das citocinas na CR (Tabela 4).

Portanto, o aumento nos níveis destas citocinas pró-inflamatórias na AR resulta em um aumento no *turnover* proteico, o que, somado às demais alterações metabólicas, caracteriza um hipermetabolismo (21,51). Este hipermetabolismo aumenta os processos catabólicos proteicos no músculo esquelético (9,57). Assim, o quadro de caquexia reumatoide é uma das mais evidentes condições clínicas que demonstram ligação entre o metabolismo e a inflamação (8)

Tabela 4 - Efeitos das citocinas na CR

Citocinas	**Efeito na CR**
TNF-α	Função metabólica de levar a perda muscular e aumento do gasto energético (9,51).
IL-1β	Contribuí para alterações metabólicas(52).
IL-6 Interferon gama (IFN-γ) Fator de crescimento transformador beta (TGF-1β) Fator de transcrição MyoD	Estas citocinas podem ativar o Fator nuclear kappa B (NF-kB)* e levar a um aumento da proteólise muscular através da via ubiquitina-proteassoma (53), o que contribui para a perda muscular que ocorre na CR (50,54,55).

* NF-kB é uma das vias de transdução de sinal mais importantes na AR, uma vez que se dedica a mediar a produção de IL-1 e TNF-α e seus efeitos em células alvo depois de terem ligado aos receptores da superfície celular (56).

2.4.1. CRITÉRIOS DE DIAGNÓSTICO, MÉTODOS DE AVALIAÇÃO E PREVALÊNCIA DE CAQUEXIA REUMATOIDE

Frequentemente, ocorre confusão sobre a definição da caquexia no contexto da AR. O termo "caquexia clássica" é usado para definir perda de peso severa, perda de gordura e músculo e aumento do catabolismo proteico devido à doença(s) subjacente(s) (16,57) e o termo CR, como descrito anteriormente, é definido como mudanças adversas na composição corporal, que envolve a redução da MLG e manutenção ou elevação da MG, induzida por um hipermetabolismo de citocinas (58,59).

Devido a esta divergência, não existe um consenso na literatura acerca dos critérios de diagnóstico para CR. Roubenoff e colaboradores utilizaram a composição corporal através de avaliação da massa celular corporal (BCM*, Body cell mass*) por medidas antropométricas e impedância bioelétrica (BIA) para diagnosticar CR(8), encontrando uma prevalência de 16% de CR. O mesmo grupo utilizou em outro estudo a avaliação de BCM por medida de contagem de potássio total no corpo (TBK, total body potassium), para diagnosticar CR(9), encontrando uma prevalência de 13%. No entanto, estes autores não estabelecem pontos de corte para as medidas propostas e não definem claramente um critério de diagnóstico para CR.

Engvall e colaboradores (14) são os primeiros autores a determinar critérios de diagnóstico para CR. Eles utilizaram IMLG abaixo do percentil 10 e IMG acima do percentil 25 e encontraram uma prevalência de CR de 18% para mulheres e 21% para homens (14). Estes critérios foram utilizados em vários outros estudos (60–64), os quais observaram uma variação de prevalência de CR de 8,0% a 53,9%. O mesmo grupo comparou estes critérios (14) (IMLG abaixo do percentil 10 e IMG acima do percentil 25) com IMLG abaixo do percentil 25 e IMG acima do percentil 50 (15), encontrando uma prevalência de CR de 18% para mulheres e 26% para homens (Tabela 5).

Concomitantemente, em um artigo de revisão incluindo pacientes com AR, Morley e colaboradores (53), estabeleceram a caquexia clássica a partir da perda de peso involuntária (5%), IMC menor que 20 naqueles com idade inferior a 65 anos de idade;IMC menor que 22 naqueles acima de 65 anos de idade; albumina menor que 3,5 g/dL, baixa MLG (10% mais baixa) e evidência de excesso de citocinas (por exemplo, PCR elevada).

Mais adiante, em 2008, Evans e colaboradores (16) estabeleceram critério mais amplo para caquexia clássica, incluindo pacientes com AR, com perda de peso de pelo menos 5% durante pelo menos 12 meses (ou IMC inferior a 20) na presença de doença subjacente e três dos seguintes critérios: diminuição da força muscular (abaixo do 3º percentil), fadiga, anorexia (ingestão calórica total inferior a 20 kcal/kg de peso corporal/dia; <70% da ingestão alimentar habitual; ou falta de apetite), baixa MLG (circunferência muscular do braço <10º percentil para idade e sexo, ou por DEXA <5,45 para as mulheres e <7,25 para os homens) ou bioquímica anormal: marcadores inflamatórios aumentados [PCR, IL-6], anemia [hemoglobina abaixo de 12 g/dL-1], e baixa albumina sérica [menor de 3,2 g/dL-1]. Entretanto, esses critérios parecem ser mais fidedignos para determinação da caquexia clássica nos pacientes oncológicos do que pacientes com AR (Tabela 5) (65).

van Bokhorst e colaboradores (65) demonstraram que apenas 1% dos pacientes com AR apresentaram caquexia a partir dos critérios de diagnósticos para caquexia clássica estabelecidos por Evans e colaboradores (16). Assim, observa-se na literatura uma variação de prevalência de CR de 1% a 53,9%.

Esta variação de prevalência de CR também é influenciada pelos métodos de avaliação escolhidos para diagnosticar esta condição, apesar de

todos os estudos citados acima utilizarem métodos de avaliação de composição corporal validado (DEXA, BIA e medidas antropométricas). Várias técnicas estão sendo usadas para avaliar a composição corporal como diluição de água, antropometria, DEXA, análise de tomografia computadorizada e ressonância Magnética, BIA e medidas antropométricas(66). No entanto, DEXA representa um método alternativo confiável, não invasivo, com melhor viabilidade, exposição mínima à radiação, alta precisão, sensibilidade e reprodutibilidade para medir MLG e MG (67,68). Entretanto é de alto custo e está restrito a grandes centros, não sendo utilizado frequentemente na rotina clínica.

Como descrito anteriormente, a CR ganhou ascensão a partir de 1992 com Roubenoff e colaboradores (8). Apesar de ser considerada uma comorbidade nova e que ainda não se tem consenso sobre definição e critérios de diagnóstico, havendo divergências sobre os dados de sua prevalência.

Tabela 5. Características dos estudos observacionais que apresentam prevalência de caquexia reumatoide (CR).

Primeiro autor	País	Tamanho amostral	Média de idade (anos)	Tempo de doença (anos)	Média do DAS28	Critério de Diagnóstico	Métodos de composição corporal	Prevalência de CR (%)
Hugo 2016(64)	França	(T=57) M: 41 H: 16	57.0 ±13.0	3.8 (3.0)	4.4 ± 1.1	Engvall et al(14)	DEXA	18.0
Maghraoui 2015(63)	Marrocos	(T=178) M: 147 H: 31	T:54.1± 11.5 M:51.8 ±10.3 H:53.3 ±10.7	8.9 (7.4)	T:4.3± 1.6 M: 4.7± 1.5 H: 4.1±0 1.4	Engvall et al(14)	DEXA	T: 53.9 M:53.7 H: 54.8
Lombard 2013(62)	Africa do Sul	(T=246) M: 204 H: 42	54.7± 13.6		NP	Engvall et al(14)	MA	10.3
Bokhorst 2012(65)	Holanda	(T=103) M:79 H: 24	*T: 60.0 (26.0-90.0)	*8.0	3.32	Evans et al(16)	BIA; força de preensão palmar; FAACT; EVA fadiga e dor; PCR; VSG; Hb;	1.0
Elkan 2009(61)	Suécia	(T=80) M: 61 H: 19	*M:60.8 (57.3–64.4) *H: 63.4 (59.8–66.9)	6.0	*M:3.3 (3.0–3.6) *H:2.6 (2.1–3.0)	Engvall et al(14)	DEXA	M: 18.0 H: 21.0
Elkan 2009(15)	Suécia	(T=80) M: 61 H: 19	*M: 60.8 (57.3-64.4) *H:63.4 (59.8-66.9)	6.0	*M:3.3 (3.0 -3.6) *H:2.6 (2.1- 3.0)	IMLG abaixo do percentil 25 e índice IMG acima do percentil 50	DEXA	M: 18.0 H: 26.0
Metsios 2009(60)	Inglaterra	(T=400) M: 292 H: 108	*+CR:68.3 (64.7–73.0) *-CR: 62.7 (54.0–69.4)	*+CR: 11.0 *-CR: 10.0	AR+CR 4.3 ± 1.8 AR-CR: 4.2 ± 1.4	Engvall et al(14)	BIA	8.5
Engvall 2008(14)	Suécia	(T=60) M: 50 H 10	*M:66.0 (63–69) *H: 60.0 (51–70)	*M:13.0 *H:16.0	*M:5.7 (5.3–6.1) *H: 4.6 (3.7–5.5)	Engvall et al(14)	DEXA	38.0

*Média; ±desvio padrão; Engvall e colaboradores(14)critério de diagnóstico IMLG abaixo do percentil 25 e índice IMG acima do percentil 50; DAS28: 28-joint disease activity score; T: total; M mulheres; H:homens; +CR: pacientes com AR e CR; −RC: pacientes com AR e sem CR; NP: não publicado; IMLG: índice de massa livre de gordura; IMG:índice de massa gorda; MA: medidas antropométricas; FAACT: the Functional Assessment of Anorexia/*Cachexia* Therapy questionnaire; EVA: escala visual analógica; PCR: proteína C reativa; VSG: velocidade de sedimentação globular; Hb: hemoglobina; DEXA: total-body dual-energy X-ray absorptiometry; BIA: bioelectrical impedance analysis

2.4.2. CAQUEXIA REUMATOIDE E DESFECHO CLÍNICO

Pacientes com AR têm um risco aumentado de morte quando comparada com população saudável (69). A inflamação da AR contribui para o surgimento de placas ateroscleróticas inflamatórias, o que pode levar ao aumento no risco de doenças cardiovasculares (DCV) (70). Este risco de DCV elevado é responsável por cerca de 40-50% da mortalidade prematura e redução da expectativa de vida entre AR em comparação com a população geral (71).

Recentemente, England e colaboradores (36) demonstraram que o IMC e a perda de peso são preditores de mortalidade por causa da AR. A perda de peso é um forte preditor de mortalidade cardiovascular e câncer, enquanto o IMC abaixo do peso é um preditor mais forte da mortalidade por consequência respiratória (36,72). A partir desta perspectiva, a CR também pode ser fator de risco independente para acelerar a morbimortalidade na AR (13).

Em 1992, Roubenoff e colaboradores (8) verificaram que baixa BCM encontrada em 67% de pacientes com AR estava inversamente associada ao número de articulações edemaciadas. Além disto, foi encontrada uma tendência de aumento de incapacidade física com diminuição da BCM após o ajuste para dor nas articulações e duração da doença. Esta redução de BCM associada a um quadro clínico inflamatório aumenta o risco de mortalidade. Segundo Dewis e colaboradores (73) e Kotler e colaboradores (74), a redução em 40% da BMC, especialmente de massa muscular, está associada à morte.

Em 1994, Roubenoff e colaboradores (9) encontraram aumento dos níveis de IL-1β e TNF-α associado a uma elevação de gasto energético basal, sugerindo que o excessivo processo inflamatório presente está relacionado ao hipermetabolismo. Além disto, eles encontraram associação inversa entre a produção de IL-1β e a ingestão dietética, sugerindo que a produção de citocinas pró-inflamatórias pode levar a uma anorexia relativa, em vez de absoluta. Em pacientes com AR, anorexia relativa induzida por IL-1β pode agravar a perda de BCM que ocorre no estado hipermetabólico, impedindo os pacientes de aumentar sua ingestão para atender às suas maiores necessidades energéticas (9). Por fim, foi encontrado níveis notavelmente mais

baixos de atividade física em sujeitos com AR em comparação com controles e níveis moderadamente menores de atividade moderada e leve.

Huffman e colaboradores (75), em um estudo recente, demonstraram que, em comparação com os controles, os pacientes com AR apresentaram concentrações musculares de proteína IL-6 75% maiores. Em pacientes com AR, as concentrações musculares de marcadores inflamatórios foram positivamente associadas com atividade da doença (IL-1β, lL-8), incapacidade (IL-1β, lL-6), dor (IL-1β, TNF-α, receptor do tipo Toll 4 (TLR, *Toll-like receptor*) e inatividade física (IL-1β, lL-6). As citocinas musculares não estavam relacionadas a citocinas sistêmicas correspondentes. Os conjuntos de genes diferencialmente expressos nos músculos na AR comparado com controles foram aqueles envolvidos nos processos de reparo do músculo esquelético e no metabolismo glicolítico. O perfil metabólico revelou concentrações 46% maiores de piruvato no músculo na AR e forte correlação positiva entre os níveis de aminoácidos envolvidos na fibrose (arginina, ornitina, prolina e glicina) e incapacidade (75). Assim, a disfunção do músculo esquelético pode contribuir para um circulo vicioso de atividade de doença, inatividade física e incapacidade física em pacientes com AR.

Engvall e colaboradores (14), em um estudo com 60 pacientes com AR, encontraram associação entre CR e atividade inflamatória, deficiência física e baixo IGF-1 biodisponível. O IGF-1 biodisponível é um importante fator anabólico na manutenção da massa muscular e na inibição da degradação protéica (76) e em níveis reduzidos associa-se ao catabolismo da proteína muscular (77). Este achado relacionado ao quadro de inflamação crônica na AR reforça a ideia que catabolismo por baixo IGF-1 e deficiência física pode desencadear a CR.

Elkan e colaboradores (61), mostraram alta frequência de CR mesmo em pacientes com atividade inflamatória moderada e função física controlada. Além disso, Elkan e colaboradores (15) analisaram associações entre dieta, composição corporal, lipídios e anticorpos naturais ateroprotetores contra a fosforilcolina (anti-PC) em pacientes com AR. Cerca de um em cada cinco pacientes com AR de baixa atividade apresentou caquexia reumatoide. Essa condição foi associada a níveis elevados de colesterol LDL, baixos níveis de

anti-PC ateroprotetor e alta frequência de hipertensão, o que é de interesse no contexto de DCV na AR. Os pacientes em uma dieta semelhante ao Mediterrâneo apresentaram altos níveis de anti-PC, apesar da frequência similar de caquexia. Altos níveis anti-PC podem fornecer alguma proteção contra DCV. Assim, as alterações de composição corporal podem levar a doenças cardiovasculares e ao aumento das morbidades, levando ao aumento do risco de morte.

Contrapondo os achados de Elkan e coladoradores(15), Metsios e colaboradores (60) não encontraram associação entre CR e pior perfil de risco de DCV, risco DCV nos 10 anos prévios, aumento da mortalidade ou prevalência de DCV. Observou-se somente elevação dos níveis de TNF-α e IL-1β, IMLG reduzida e diminuição dos níveis de albumina sérica no grupo de pacientes AR com CR, comparados ao grupo de pacientes AR sem CR.

El Maghraoui e colaboradores (63) encontraram associação entre CR com atividade da doença e baixa densidade mineral óssea de quadril. Sabe-se que baixa densidade mineral óssea está associada ao aumento de quedas e consequentemente, com o aumento da mortalidade. Ainda, os autores (63) demonstraram que a maior parte dos pacientes apresentou sobrepeso ou obesidade, o que pode levar a complicações cardiovasculares, diabetes melittus tipo II e hipertensão. Estes achados corroboram com a associação entre CR e aumento das comorbidades e morbimortalidade em pacientes com AR.

Mais recentemente, Hugo e colaboradores (64) não encontraram associação entre CR e síndrome metabólica em pacientes AR com atividade da doença moderada. Contudo, a partir dos estudos citados acima, é evidenciado que não se tem um consenso sobre o impacto da presença da CR no prognóstico de pacientes com AR. Este fato ressalta a necessidade de aprofundamento da investigação da CR, particularmente através de estudos longitudinais.

2.4.3. ESTRATÉGIAS TERAPÊUTICAS PARA CAQUEXIA REUMATOIDE

Diversas estratégias terapêuticas estão sendo testadas a fim de minimizar as consequências da CR. Tratamento medicamentoso, dieta e exercício físico são as estratégias mais observadas na literatura.

2.4.3.1. Terapia medicamentosa

As drogas modificadoras do curso da doença (DMCD) e as drogas biológicas são utilizadas como tratamento para a AR. Apesar de sua eficácia no controle da doença, existem poucas evidências acerca de seus efeitos sobre a CR. Até o momento, poucos estudos verificando os efeitos dos tratamentos biológicos, especificamente anti-TNF e inibidor de IL-6, na CR estão descritos na literatura.

O efeito do tratamento com anti-TNF na composição corporal de pacientes com AR tem sido estudado, porém, ainda não se tem um resultado definitivo (78–83). Alguns estudos descrevem que o tratamento com anti-TNF parece aumentar o peso corporal, MLG e MG (78–80). Além disto, o tratamento com anti-TNF parece restaurar a resposta anabólica normal à alimentação na caquexia independente de uma redução genérica da inflamação sistêmica (78–80). Contrapondo estes achados, três estudos descrevem que o tratamento com anti-TNF não altera de forma positiva a composição corporal (81–83).

Quanto ao efeito do tratamento com inibidor de IL-6 na composição corporal, apenas um estudo foi encontrado. Tournadre e colaboradores (84) investigaram os efeitos do tocilizumab (TCZ), um anticorpo monoclonal bloqueador do receptor da IL-6, na composição corporal e perfil metabólico em pacientes tratados com AR. Apesar de ser encontrado um aumento de peso corporal durante o tratamento com TCZ, não houve aumento da gordura. No entanto, uma modificação na distribuição de gordura foi observada. Em contraste, o ganho muscular sugere que o bloqueio da IL-6 pode ser eficiente no tratamento da sarcopenia associada à AR (84). Essas observações devem ser reproduzidas em novos estudos, com amostras maiores e, preferentemente, com grupos controles.

Não existem estudos avaliando primariamente o tratamento medicamentoso para CR. Considerando que a CR é uma condição que leva ao aumento de diversas comorbidades, como citado no capítulo anterior, se faz necessário a avaliação dessa comorbidade em ensaios clínicos randomizados de novos fármacos, bem como sua avaliação nos estudos de fase IV a fim de estabelecer se existem diferenças entre os fármacos modificadores do curso da doença em seus efeitos sobre a CR.

2.4.3.2. Exercício físico

O exercício resistido tem sido um tratamento não farmacológico seguro em pacientes com AR para diminuir os efeitos da caquexia e, como consequência, restauração da massa muscular e melhora substancial da função física (85–90). Ensaios clínicos randomizados e controlados têm demonstrado que treinamentos resistido, de alta intensidade, progressivos e com duração entre 6 e 24 semanas não aumentam o dano radiográfico das articulações grandes (85–90). Além disto, são eficazes para estimular o crescimento muscular, reduzir a massa gorda e melhorar a função física de pacientes com AR(85–90).

Com outra metodologia de treinamento físico, estudos têm demonstrado que treinamentos combinados (exercícios aeróbico + exercícios resistidos) também aumentam a aptidão física e massa muscular, além de diminuir a gordura subcutânea (91,92).

Portanto, a partir dos estudos citados acima, é possível concluir que o treinamento resistido e combinado são ferramentas não-farmacológica seguras e eficazes para diminuir os efeitos da CR em paciente com AR sem prejudicar a atividade da doença. De fato, recentemente o EULAR publicou recomendações para atividade física em pacientes com artropatias inflamatórias, considerando que devem ser parte integral do tratamento padrão durante todo o curso dessas doenças(93).

2.4.3.3. Dieta

Pacientes com AR não têm deficiência na ingestão de proteína ou energia. No entanto, baixos níveis de atividade física e gasto energético favorecem o acúmulo de MG (8,9,51,94,95).

Em 1996, Engelhart e colaboradores (96) realizaram um estudo para verificar o efeito da redução no consumo de energia na dieta, suplementação de proteína com alta e baixa energia e treinamento físico moderado. Assim, eles concluíram que o tratamento proposto foi eficaz para alcançar uma perda de peso significativa com perda mínima de BCM e manutenção da aptidão física.

Um ensaio clínico randomizado e controlado (97) foi realizado para investigar a eficácia de uma mistura de b-hidroxi-b-metilbutirato, glutamina e arginina (HMB/GLN/ARG) como tratamento nutricional para CR e foi demonstrado que a suplementação dietética com HMB/GLN/ARG foi melhor tolerada, mas não foi mais eficaz na reversão da caquexia em pacientes com AR em comparação com a mistura de outros aminoácidos não essenciais usados como placebo.

Mais recentemente, um ensaio clínico randomizado (98) verificou a eficácia da suplementação oral de creatina (Cr) no aumento da massa , força e a função física em pacientes com AR. Os autores concluíram que nos pacientes com AR, a suplementação de Cr não teve efeitos adversos relacionados ao tratamento, sugerindo que a suplementação de Cr pode oferecer tratamento adjunto aceitável para atenuar a perda muscular e assim, este tratamento pode ser benéfico para pacientes que tem CR grave.

Na literatura, são escassos estudos de intervenções nutricionais em pacientes com CR. Assim é necessário investigar quais intervenções dietéticas podem beneficiar pacientes com CR.

3. MARCO TEÓRICO

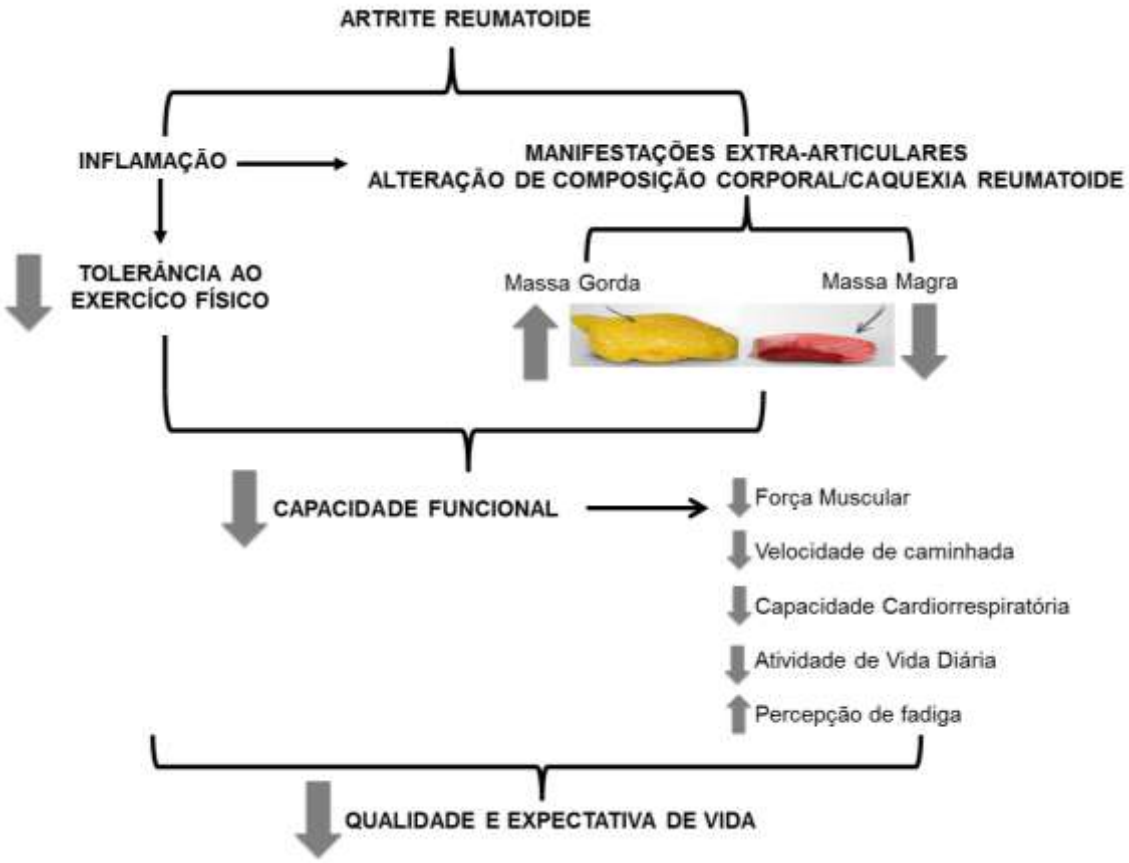


Figura 3. Marco teórico

4. JUSTIFICATIVA

A CR é uma manifestação extra-articular frequente na AR. Atualmente ela é descrita pelas alterações da composição corporal sem levar em consideração parâmetros de capacidade funcional ou a presença de biomarcadores. Mesmo não se conhecendo com exatidão a taxa de pacientes com AR acometidos por esta condição, é sabido que ela impacta negativamente na doença e que não existe um consenso sobre o melhor tratamento. Assim, a padronização quanto à definição, critérios de diagnósticos e método de avaliação de CR são necessários para análise situacional precisa. Além disto, são necessários estudos longitudinais para que se demonstre a relação da CR com os desfechos clínicos e assim impactar em um manejo clínico eficaz.

5. OBJETIVOS

5.1. OBJETIVO PRINCIPAL

Avaliar a prevalência de caquexia e fatores associados a esta condição em pacientes com artrite reumatoide.

5.2. OBJETIVOS ESPECÍFICOS

Artigo 1

- Avaliar a prevalência estimada de CR nos estudos publicados;

Artigo 2

- Avaliar a prevalência de caquexia por três critérios de diagnóstico em pacientes com AR;

- Avaliar as alterações dos parâmetros incluídos nos critérios de caquexia reumatoide e caquexia clássica ao longo de 12 meses;

- Avaliar as alterações de outros fatores clínicos e laboratoriais relacionados à caquexia reumatoide e caquexia clássica ao longo de 12 meses.

6. REFERÊNCIAS DA REVISÃO DA LITERATURA

1. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Prim. 2018;4:18001.
2. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;358:903–11.
3. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388(10055):2023–38.
4. Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. Lancet (London, England). 2010;376(9746):1094–108.
5. Marques Neto JF, Gonçalves ET, Langen LF de OB, Cunha M de FL, Radominski S, Oliveira SM de, et al. Estudo multicêntrico da prevalência da artrite reumatóide do adulto em amostras da populaçao brasileira. Rev bras Reum. 33(5):169–73.
6. Alamanos Y, Drosos A. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev. 2005;4(3):130–6.
7. Walsmith J, Abad L, Kehayias J, Roubenoff R. Tumor necrosis factor-alpha production is associated with less body cell mass in women with rheumatoid arthritis. J Rheumatol. 2004;31(1):23–9.
8. Roubenoff R, Roubenoff RA, Ward LM, Holland SM, Hellmann DB. Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. J Rheumatol. 1992;19(10):1505–10.
9. Roubenoff R, Roubenoff R a, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest. 1994;93(6):2379–86.
10. Roubenoff R, Rall LC. Humoral mediation of changing body composition during aging and chronic inflammation. Nutr Rev. 1993;51:1–11.
11. Rall LC, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. Rheumatology. 2004;43(10):1219–23.
12. Roubenoff R. Rheumatoid cachexia: a complication of rheumatoid arthritis moves into the 21st century. Arthritis research & therapy. 2009. p. 108.
13. Walsmith J, Roubenoff R. Cachexia in rheumatoid arthritis. Int J Cardiol. 2002;85(1):89–99.
14. Engvall IL, Elkan AC, Tengstrand B, Cederholm T, Brismar K, Hafstrom I. Cachexia in rheumatoid arthritis is associated with inflammatory activity, physical disability, and low bioavailable insulin-like growth factor. Scand J Rheumatol. 2008;37(5):321–8.
15. Elkan A-C, Hakansson N, Frostegard J, Cederholm T, Hafstrom I. Rheumatoid cachexia is associated with dyslipidemia and low levels of

atheroprotective natural antibodies against phosphorylcholine but not with dietary fat in patients with rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther. 2009;11(2):R37.

16. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: A new definition. Clin Nutr. 2008;27(6):793–9.

17. Santo RCE, Fernandes KZ, Lora PS, Filippin LI, Xavier RM. Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2018;

18. Mota LMH, Cruz BA, Brenol CV, Pereira IA, Fronza LSR, Bertolo MB, et al. Consenso da Sociedade Brasileira de Reumatologia 2011 para o diagnóstico e avaliação inicial da artrite reumatoide Licia. Rev Bras Reum. 2011;51(3):199–219.

19. Costa JO, Almeida AM, Junior AAG, Cherchiglia ML, Andrade EIG, Acurcio F de A. Análise de custo do tratamento medicamentoso da artrite reumatóide. Cad Saúde Pública. 2008;44.

20. Costa J de O, Almeida AM, Junior AAG, Cherchiglia ML, Andrade EIG, Acurcio F de A. Tratamento da artrite reumatoide no Sistema Único de Saúde , Brasil : gastos com infliximabe em comparação com medicamentos modificadores do curso da doença sintéticos , 2003 a 2006. Cad Saúde Pública. 2014;30(2):283–95.

21. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205–19.

22. Kondo Y, Yokosawa M, Kaneko S, Furuyama K, Segawa S, Tsuboi H, et al. Transcriptional Regulation of CD4 + T Cell Differentiation in Experimentally Induced Arthritis and Rheumatoid Arthritis. 2018;70(5):653–61.

23. Bustamante MF, Garcia-carbonell R, Whisenant KD, Guma M. Fibroblast-like synoviocyte metabolism in the pathogenesis of rheumatoid arthritis. 2017;1–12.

24. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology (Oxford). 2012;51(5):3–11.

25. Deal C. Bone Loss in Rheumatoid Arthritis : Systemic , Periarticular and Focal. Curr Rheumatol Rep. 2012;14(3):231–7.

26. Loza E, Lajas C, Luis J, Alejandro A, Isidoro B, Álvaro G, et al. Consensus statement on a framework for the management of comorbidity and extra articular manifestations in rheumatoid arthritis. Rheumatol Int. 2015;35(3):445–58.

27. Pappas DA, Nyberg F, Kremer JM, Lampl K, Reed GW, Horne L, et al. Prevalence of cardiovascular disease and major risk factors in patients with rheumatoid arthritis : a multinational cross-sectional study. Clin Rheumatol. 2018;

28. Raemdonck K Van, Umar S, Szekanecz Z, Zomorrodi RK, Shahrara S. Impact of obesity on autoimmune arthritis and its cardiovascular complication. Autoimmun Rev. 2018;17(8):821–35.

29. Hellgren K, Baecklund E, Backlin C, Sundstrom C, Smedby KE, Askling J. Rheumatoid Arthritis and Risk of Malignant Lymphoma Is the Risk Still Increased ? Arthritis Rheumatol. 2017;69(4):700–8.

30. Brito Y, Glassberg MK, Ascherman DP. Rheumatoid Arthritis-Associated Interstitial Lung Disease : Current Concepts. Curr Rheumatol Rep. 2017;19(12):79.

31. Zamora-legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Patterns of interstitial lung disease and mortality in rheumatoid arthritis. Rheumatology. 2016;56(3):344–50.

32. Baker JF, Long J, Mostoufi-moab S, Denburg M, Jorgenson E, Sharma P, et al. Muscle Deficits in Rheumatoid Arthritis Contribute to Inferior Cortical Bone Structure and Trabecular Bone Mineral Density. J Rheumatol. 2017;44(12):1777–85.

33. Peng J, Gong Y, Zhang Y, Xiao Z, Zeng Q, Chen S. Bone Mineral Density in Patients With Rheumatoid. 2016;22(2):71–4.

34. Marques WV, Cruz VA, Rego J, Silva NA da. The impact of comorbidities on the physical function in patients with rheumatoid arthritis. Rev Bras Reum. 2016;56(1):14–21.

35. Radner H, Smolen JS, Aletaha D. Comorbidity affects all domains of physical function and quality of life in patients with rheumatoid arthritis. Rheumatology. 2011;50:381–8.

36. Bryant R. England., Joshua F. Baker, Harlan Sayles, Kaleb Michaud, Liron Caplan, Lisa A. Davis. Body Mass Index, Weight Loss, and Cause-Specific Mortality in Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2018;70(1):11–8.

37. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.

38. van der Heijde DM, van ’t Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990;49(11):916–20.

39. Prevoo ML, van ’t Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44–8.

40. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al.

A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatol. 2003;42(2):244–57.

41. Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. Best Pr Res Clin Rheumatol. 2007;21(4):663–75.

42. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Cl. Arthritis Care Res. 2011;63(11):S14-36.

43. Farheen K, Agarwal S. Assessment of Disease Activity and Treatment Outcomes in Rheumatoid Arthritis. J Manag Care Pharm. 2011;17(9):S9-13.

44. Steinbrocker O, Traeger C, Batterman R. Therapeutic criteria in rheumatoid arthritis. JAMA. 1949;140(8):659–62.

45. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum. 1992;35(5):498–502.

46. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). 2005;

47. Paget J. Clinical Lectures on the nervous mimicry of organic disease,. Lancet. 1873;102(2615):511–3.

48. Westhovens R, Nijs J, Taelman V, Dequeker J. Body composition in rheumatoid arthritis. Br J Rheumatol. 1997;36(4):444–8.

49. Teixeira ONV, Filippin LI, Viacava PR, Oliveira PG, Xavier RM. Muscle wasting in collagen-induced arthritis and disuse atrophy. Exp Biol Med (Maywood). 2013;238(12):1421–30.

50. Metsios GS, Kalinoglou AS, Koutedakis Y, Kitas GD. Rheumatoid Cachexia: causes, significance and possible interventions. Hosp Chronicles. 2006;1(1):20–6.

51. Rall LC, Rosen CJ, Dolnikowski G, Hartman WJ, Lundgren N, Abad LW, et al. Protein metabolism in rheumatoid arthritis and aging. Effects of muscle strength training and tumor necrosis factor alpha. Arthritis Rheum. 1996;39(7):1115–24.

52. Dinarello CA. Interleukin-1 and the Pathogenesis of the Acute-Phase Response. N Engl J Med. 1984;311(22):1413–8.

53. Morley JE, Thomas DR, Wilson M-MG. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr. 2006;83(4):735–43.

54. Mitch WE, Goldberg AL. Mechanisms of Muscle Wasting — The Role of the Ubiquitin–Proteasome Pathway. N Engl J Med. 1996;335(25):1897–905.

55. Li Y-P, Lecker SH, Chen Y, Waddell ID, Goldberg AL, Reid MB. TNF-alpha increases ubiquitin-conjugating activity in skeletal muscle by up-regulating UbcH2/E220k. FASEB J. 2003;17(9):1048–57.

56. Arend WP. Physiology of cytokine pathways in rheumatoid arthritis. Arthritis Rheum. 2001;45(1):101–6.

57. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by Special Interest Groups (SIG) " cachexia-anorexia in chronic wasting diseases" and " nutrition in geriatrics." Clin Nutr. 2010;29(2):154–9.

58. Summers GD, Deighton CM, Rennie MJ, Booth AH. Rheumatoid cachexia: A clinical perspective. Rheumatol. 2008;47(8):1124–31.

59. Lemmey AB. Rheumatoid cachexia: The undiagnosed, untreated key to restoring physical function in rheumatoid arthritis patients? Rheumatol. 2016;55(7):1149–50.

60. Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, Sandoo A, Toms TE, Nevill AM, et al. Rheumatoid cachexia and cardiovascular disease. Clin Exp Rheumatol. 2009;27(6):985–8.

61. Elkan A-C, Engvall I-L, Cederholm T, Hafstr?m I. Rheumatoid cachexia, central obesity and malnutrition in patients with low-active rheumatoid arthritis: feasibility of anthropometry, Mini Nutritional Assessment and body composition techniques. Eur J Nutr. 2009;48(5):315–22.

62. Lombard LA, Plessis LM, Visser J. Body composition of rheumatoid arthritis patients in the City of Cape Town , South Africa. Clin Rheumatol. 2014;33(4):467–76.

63. El Maghraoui A, Sadni S, Rezqi A, Bezza A, Achemlal L, Mounach A. Does rheumatoid cachexia predispose patients with rheumatoid arthritis to osteoporosis and vertebral fractures? J Rheumatol. 2015;42(9):1556–62.

64. Hugo M, Cetre NM, Pierreisnard A, Schaeverbeke T, Gin H, Rigalleau V. Energy expenditure and nutritional complications of metabolic syndrome and rheumatoid cachexia in rheumatoid arthritis: An observational study using calorimetry and actimetry. Rheumatol. 2016;55(7):1202–9.

65. van Bokhorst - de van der Schueren MAE, Konijn NPC, Bultink IEM, Lems WF, Earthman CP, van Tuyl LHD. Relevance of the new pre-cachexia and cachexia definitions for patients with rheumatoid arthritis. Clin Nutr. 2012;31(6):1008–10.

66. Tewari N, Awad S, Macdonald IA, Lobo DN. A comparison of three methods to assess body composition. Nutrition. 2018;47:1–5.

67. Lee SY, Gallagher D. Assessment methods in human body composition. Curr Opin Clin Nutr Metab Care. 2008;11(5):566–72.

68. Kanellakis S, Manios Y. Validation of five simple models estimating body

fat in white postmenopausal women use in clinical practice and research. Obesity. 2012;20(6):1329–32.

69. Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, et al. Survival in rheumatoid arthritis: A population-based analysis of trends over 40 years. Arthritis Rheum. 2003;48(1):54–8.

70. Full LE, Ruisanchez C, Monaco C. The inextricable link between atherosclerosis and prototypical inflammatory diseases rheumatoid arthritis and systemic lupus erythematosus. Arthritis Res Ther. 2009;11(2):217.

71. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2012;71(9):1524–9.

72. Baker Joshua F, Billig Erica, Michaud Kaleb, Ibrahim Said CL, W CG, Stokes A. Weight Loss, the Obesity Paradox, and the Risk of Death in Rheumatoid Arthritis. Arthritis Rheumatol. 2015;67(7):1711–7.

73. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69(4):491–7.

74. Kotler DP, Tierney AR, Wang J, Pierson RN. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. Am J Clin Nutr. 1989;50(3):444–7.

75. Huffman KM, Jessee R, Andonian B, Davis BN, Narowski R, Huebner JL, et al. Molecular alterations in skeletal muscle in rheumatoid arthritis are related to disease activity, physical inactivity, and disability. Arthritis Res Ther. 2017;19:12.

76. Fryburg DA. Insulin-like growth factor I exerts growth hormone- and insulin-like actions on human muscle protein metabolism. Am J Physiol. 1994;267(2 Pt 1):E331-6.

77. Frost RA, Lang CH. Growth factors in critical illness: regulation and therapeutic aspects. Curr Opin Clin Nutr Metab Care. 1998;1(2):195–204.

78. Toussirot E, Mourot L, Dehecq B, Wendling D, Grandclément E, Dumoulin G. TNFα blockade for inflammatory rheumatic diseases is associated with a significant gain in android fat mass and has varying effects on adipokines: a 2-year prospective study. Eur J Nutr. 2014;53:951–61.

79. Chen C-Y, Tsai C-Y, Lee P-C, Lee S-D. Long-term etanercept therapy favors weight gain and ameliorates cachexia in rheumatoid arthritis patients: roles of gut hormones and leptin. Curr Pharm Des. 2013;19(10):1956–64.

80. Engvall I-L, Tengstrand B, Brismar K, Hafstr?m I. Infliximab therapy increases body fat mass in early rheumatoid arthritis independently of

changes in disease activity and levels of leptin and adiponectin: a randomised study over 21 months. Arthritis Res Ther. 2010;12(5):R197.

81. Marcora SM, Chester KR, Mittal G, Lemmey AB, Maddison PJ. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr. 2006 Dec;84(6):1463–72.

82. Metsios GS, Stavropoulos-kalinoglou A, Douglas KMJ, Koutedakis Y, Nevill AM, Panoulas VF, et al. Blockade of tumour necrosis factor-α in rheumatoid arthritis: Effects on components of rheumatoid cachexia. Rheumatology. 2007;46(12):1824–7.

83. Serelis J, Kontogianni MD, Katsiougiannis S, Bletsa M, Tektonidou MG, Skopouli FN. Effect of anti-TNF treatment on body composition and serum adiponectin levels of women with rheumatoid arthritis. Clin Rheumatol. 2008;27(6):795–7.

84. Tournadre A, Pereira B, Dutheil F, Giraud C, Courteix D, Sapin V, et al. Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. J Cachexia Sarcopenia Muscle. 2017;8(4):639–46.

85. De Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis Rheum. 2003;48(9):2415–24.

86. Marcora SM, Lemmey AB, Maddison PJ. Can progressive resistance training reverse cachexia in patients with rheumatoid arthritis? Results of a pilot study. J Rheumatol. 2005;32(6):1031–9.

87. Lemmey AB, Marcora SM, Chester K, Wilson S, Casanova F, Maddison PJ. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial. Arthritis Rheum. 2009;61(12):1726–34.

88. Sharif S, Thomas JM, Donley DA, Gilleland DL, Bonner DE, Mccrory JL, et al. Resistance Exercise Reduces Skeletal Muscle Cachexia and Improves Muscle Function in Rheumatoid Arthritis. Case Rep Med. 2011;2011:205691.

89. Lemmey AB, Williams SL, Marcora SM, Jones J, Maddison PJ. Are the benefits of a high-intensity progressive resistance training program sustained in rheumatoid arthritis patients? A 3-year followup study. Arthritis Care Res. 2012;64(1):71–5.

90. Morsley K, Berntzen B, Erwood L, Bellerby T, Williamson L. Progressive resistance training (PRT) improves rheumatoid arthritis outcomes: A district general hospital (DGH) model. Musculoskeletal Care. 2018;16(1):13–7.

91. Häkkinen A, Pakarinen A, Hannonen P, Kautiainen H, Nyman K, Kraemer W, et al. Effects of prolonged combined strength and endurance training

on physical fitness, body composition and serum hormones in women with rheumatoid arthritis and in healthy controls. Clin Exp Rheumatol. 2005;23(4):505–12.

92. Strasser B, Leeb G, Strehblow C, Schobersberger W, Haber P, Cauza E. The effects of strength and endurance training in patients with rheumatoid arthritis. Clin Rheumatol. 2011;30(5):623–32.

93. Rausch Osthoff AK, Niedermann K, Braun J, Adams J, Brodin N, Dagfinrud H, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis. 2018;77(9):1251–60.

94. Roubenoff R, Walsmith J, Lundgren N, Snydman L, Dolnikowski GJ, Roberts S. Low physical activity reduces total energy expenditure in women with rheumatoid arthritis: implications for dietary intake recommendations. Am J Clin Nutr. 2002;76(4):774–9.

95. Roubenoff R, Roubenoff RA, Ward LM, Stevens MB. Catabolic effects of high-dose corticosteroids persist despite therapeutic benefit in rheumatoid arthritis. Am J Clin Nutr. 1990;52(6):1113–7.

96. Engelhart M, Kondrup J, Høie LH, Andersen V, Kristensen JH, Heitmann BL. Weight reduction in obese patients with rheumatoid arthritis, with preservation of body cell mass and improvement of physical fitness. Clin Exp Rheumatol. 14(3):289–93.

97. Marcora S, Lemmey A, Maddison P. Dietary treatment of rheumatoid cachexia with beta-hydroxy-beta-methylbutyrate, glutamine and arginine: a randomised controlled trial. Clin Nutr. 2005;24(3):442–54.

98. Wilkinson TJ, Lemmey AB, Jones JG, Sheikh F, Ahmad YA, Chitale S, et al. Can Creatine Supplementation Improve Body Composition and Objective Physical Function in Rheumatoid Arthritis Patients? A Randomized Controlled Trial. Arthritis Care Res (Hoboken). 2016;68(6):729–37.

7. ARTIGOS

7.1. ARTIGO 1: Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis

Periódico: Journal of Cachexia, Sarcopenia and Muscle (2018)

Status: Publicado

Fator de impacto: 12,5

Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis

Rafaela C.E. Santo [1,2,3], Kevin Z. Fernandes[1,4] , Priscila S. Lora[1,5] ,Lidiane I. Filippin [1,6] & Ricardo M. Xavier [1,2,3*]

[1]Hospital de Clínicas de Porto Alegre, Laboratório de Doenças Autoimunes, Porto Alegre, Brazil,

[2] Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Porto Alegre, Brazil,

[3] Hospital de Clínicas de Porto Alegre, Serviço de Reumatologia, Porto Alegre, Brazil,

[4] Centro Universitário Metodista IPA, Porto Alegre, Brazil,

[5] Universidade do Vale do Rio dos Sinos, São Leopoldo, Brazil,

[6] Universidade La Salle, Canoas, Brazil.

*Correspondence to: Ricardo M. Xavier, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, R. Ramiro Barcelos, 2350, Porto Alegre, 90035-003, Brazil. Phone: +55 51 3359 8837, Fax: +55 51 3359 8340, Email: rxavier10@gmail.com

ABSTRACT

Background: Low muscle mass occurs in patients with rheumatoid arthritis without weight loss, this condition is referred as rheumatoid cachexia. The aim of the current study was perform a systematic review with meta-analysis to determine the rheumatoid cachexia prevalence.

Methods: A systematic review with meta-analysis of observational studies published in English, between 1994 and 2016 was conducted using MEDLINE (via PubMed) and other relevant sources. Search strategies were based on pre-defined keywords and medical subject headings (MeSH). The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale. Meta- analysis was used to estimate the prevalence and because studies reported different methods and criteria to estimate body composition and prevalence of rheumatoid cachexia, subgroup analyses were performed. Meta-regression adjusted for the 28-joint disease activity score and disease duration (years) was performed (significance level at $p \leq 0.05$).

Results: Of 136 full articles (one duplicate publication) screened for inclusion in the study, eight were included. The estimated overall prevalence of rheumatoid cachexia was 19% (95% CI 07-33%). This prevalence was 29% (95% CI 15-46%) when body composition was measured by dual-energy X-ray absorptiometry. When the diagnostic criteria was fat-free mass index below the 10th percentile and fat mass index above the 25th percentile, rheumatoid cachexia prevalence was 32% (95% CI 14-52%). The 28-joint disease activity score and disease duration had no influence on the estimated prevalence of rheumatoid cachexia ($p>0.05$). Most studies were rated as having moderate methodological quality. Conclusion: Meta-analysis showed a prevalence of rheumatoid cachexia of 15 to 34%, according to different criteria, demonstrating that this condition is a frequent comorbidity of rheumatoid arthritis. To better understand its clinical impact, more studies using standardized definitions and prospective evaluations are urgently needed.

Keywords: Cachexia; Rheumatoid Cachexia; Sarcopenia; Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by chronic, symmetric, and erosive synovitis that may lead to severe disability and premature death [1-3]. In addition to joint damage, changes in body composition have been observed in patients with RA, including reduced fat-free mass (FFM), of which muscle mass is the major component, with or without loss of fat mass (FM), resulting in no or limited changes in body mass index (BMI) [4,5]. This condition has been referred to as rheumatoid cachexia (RC) [6-8].

The definition of ‘cachexia’ (classic cachexia), ‘sarcopenia’, ‘sarcopenic obesity’ and ‘RC’ are diverse in the available literature. Sarcopenia (Greek ‘sarx’ or flesh and ‘penia’ or loss) is currently used to characterize the combination of low muscle mass and function (strength and performance) [9,10], while sarcopenic obesity refers to the copresence of both sarcopenia and obesity. Classic cachexia (Greek ‘kako`s’ or bad and ‘he´xis’ or condition) is a term used to

characterize the condition involving severe loss of weight, fat, and muscle mass and increased protein catabolism due to underlying disease(s) [11,12]. Roubenoff et al [5,13] described a common reduction in total body cell mass (BCM) in patients with RA and referred to this condition as rheumatoid cachexia. BCM consists primarily of muscle mass, with visceral mass (serum proteins, erythrocytes, granulocytes, lymphocytes, liver, kidneys, pancreas, heart) and immune cell mass contributing lesser amounts. Also, this author considers FM, extracellular water, connective tissue (cartilage, fibrous tissues and skeletal tissues) and bone, components not included in BCM. However, recently Engvall et al described RC as adverse changes in body composition (reduced FFM with or without loss of FM) in patients with RA [14,15].

Excess of pro-inflammatory cytokines as IL-1 beta and TNF-alpha are considered to be the central feature in RC [5]. In addition, as for clinical outcomes, RC has been associated with an increased risk of physical disability, morbidity, and mortality [16,17].

Despite several publications on RC, there is no consensus on the clinical criteria for its diagnosis [18], leading to considerable variability in reports of RC prevalence. Attempts have been made to diagnose RC based on body composition measured by different methods, including computed tomography, magnetic resonance imaging, dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), and anthropometric methods. In addition to different methods to evaluate body composition, different criteria have been used to diagnose RC (5,11). Therefore, the diagnostic criteria used for RC and the method used to measure body composition can greatly impact the estimation of RC prevalence, but this has not been systematically studied. The aim of the current study was to systematically review the literature and estimate the RC prevalence.

METHODS

We conducted this systematic review with meta-analysis in accordance with PRISMA guidelines [19] after registering the protocol with PROSPERO (CRD42017073495).

Data sources. An electronic search was performed using MEDLINE (via PubMed) and other relevant sources. We used a comprehensive search strategy tailored to each database.

Search terms. Keywords and medical subject headings (MeSH) for the terms “rheumatoid arthritis”, “arthritis”, “arthritis rheumatoid” AND “cachexia” AND “sarcopenia” were selected.

Inclusion/Exclusion criteria. Cross-sectional and cohort studies were included in the systematic review and meta-analysis. Studies on experimental models, randomized controlled trials, reviews, studies on other diseases or topics, and studies without prevalence data of rheumatoid cachexia were excluded. In addition, studies that evaluated only muscle mass, without providing data on FM, were excluded.

Data extraction. Title, abstract, and full-text screening was performed in duplicate by two independent reviewers (Santo, RCE and Fernandes, KZ). The reviewers independently extracted data from the studies using a pre-established data extraction form, which is available

upon request. All study data were recorded using a bibliographic management program (Mendeley®, version 1.17.9). Disagreements about data abstraction were resolved by discussion between the two reviewers. If no agreement could be reached, a third and fourth reviewers (Filippin, L and Lora, P) provided the final decision. Information extracted during data abstraction included author names, date of publication, journal of publication, number of study participants, age range of population, type of population, definition of RC (with method(s) of body composition assessment, cutoff points, and reference population), and RC prevalence (percentage or number of participants with and without RC).

Strategy for data synthesis. The Newcastle-Ottawa Scale (NOS), adapted for cross-sectional studies, was used to assess methodological quality of sampling, selection, exposure, and clinical outcomes of the studies selected. Using the NOS, each study was judged on seven items categorized into three groups: selection of study groups; comparability of groups; and ascertainment of either the exposure or outcome of interest. The maximum possible score was 10 stars, which represented the highest methodological quality [20]. Studies awarded 7–10 stars were rated as having high quality; 5–6 stars, as having moderate quality; and <5 stars, as having low quality[21]. Studies were include independently of the methodological quality calculated. Meta-analysis was performed using Stata® 11.0. The prevalence of RC (with 95% confidence intervals [CI]) was estimated using random effect adjust and Freeman-Tukey. Double Arcsine Transformation (FFT). The I^2 statistic was used to assess heterogeneity among studies. Meta-regression adjusted for the 28-joint disease activity score (DAS28) and disease duration (years) was performed, and the significance level was set $p \leq 0.05$. All analyses were perfomed using the metaprop command in Stata.

RESULTS

Search strategy

We identified 136 potentially relevant full articles (one duplicate publication) based on the search strategy described at the initial search stage. Figure 1 shows the flow diagram of study selection. After title, abstract, and full-text screening, 127 articles were excluded (25 experimental model; 40 reviews; 10 clinical trials; 10 other populations; 26 other topics; and, 16 without prevalence of rheumatoid cachexia) in according with inclusion/exclusion criteria. Therefore, eight relevant full articles were included in the review and incorporated into the meta-analysis.

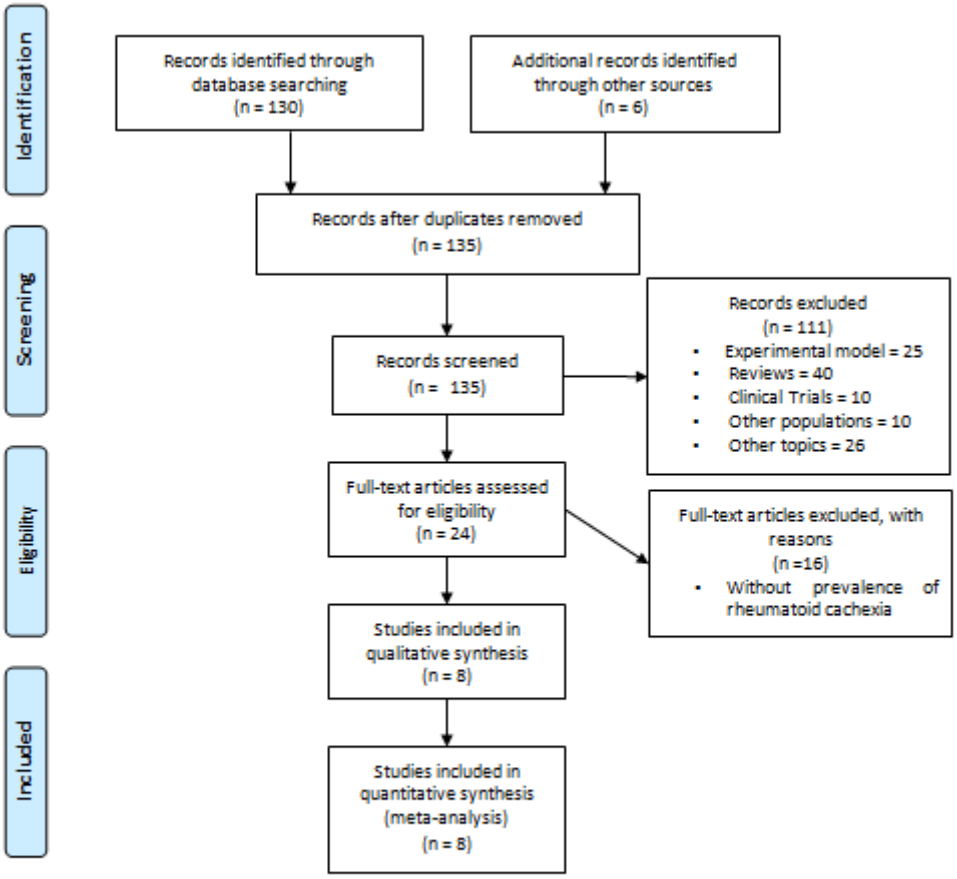


Figure 1. Flow diagram of search results and study selection

Characteristics of the studies

All included studies were published between 2008 and 2016. Sample sizes ranged from 50 to 400 patients, with a female predominance. Mean age ranged from 54.1 to 65.0 years. DAS28 ranged from 3.1 to 5.2. The characteristics of the included studies are summarized in Table 1. All studies had a cross-sectional design. Most studies were conducted in European populations, while one was from Morocco and another was from South Africa.

Diagnostic criteria for RC

Most studies used only body composition parameters as diagnostic criteria for RC. Fat-free mass index (FFMI) below the 10th percentile and fat mass index (FMI) above the 25th percentile, as proposed by Engvall et al [14], were used as diagnostic criteria for RC in six (75.0%) of eight included studies [14,22-28]. Of the remaining two studies, one used the diagnostic criteria proposed by Elkan et al of FFMI below the 25th percentile and FMI above the 50th percentile [23], and the other used the diagnostic criteria proposed by Evans et al, that includes another parameters besides body composition (body weight loss of 5% or more within 12 months (or a BMI ≤20 kg/m^2) and at least three of the following factors: decreased muscle

strength; fatigue; anorexia; low FMI; and abnormal biochemistry (increased inflammatory markers [CRP, IL-6], anemia [Hb <12 g/dL], low serum albumin [<3.2 g/dL])) [11].

Methods of body composition assessment for RC

Of eight included articles, five (62.5%) used total-body DEXA, two (25.0%) used BIA [22, 25], and one (12.5%) used anthropometric measurements [26].

RC prevalence

RC prevalence ranged from 1.0 to 53.9% (Table 1). Maghraoui et al [27] found the highest prevalence using the diagnostic criteria for RC proposed by Engvall et al [14], while Bokhorst et al [25] found the lowest prevalence using the diagnostic criteria for cachexia proposed by Evans et al [11].

Meta-analysis

In the overall meta-analysis (body composition as the only criterion), RC prevalence estimated was 19% (95% CI 07-33%) with I^2 =96.74%, p=0.00(Figure 2). Two subgroup analysis were performed. When body composition determine by DEXA, RC prevalence was estimated at 29% (95% CI 15-46%) with I^2 =92.63%, p=0.00 (Figure 3) and when FFMI below the 10th percentile and FMI above the 25th percentile were used as diagnostic criteria, RC prevalence estimated was estimated 32% (95% CI 14-52%) with I^2 =93.24%, p=0.00 (Figure 4). In the meta-regression model, neither DAS28 nor age had an influence on the RC estimated prevalence (p=0.545, SEM=0.04; and p=0.614, SEM=0.02, respectively).

Table 1. Characteristics of included studies.

First author name	Country	Sample size	Mean age (years)	Disease duration (years)	Mean DAS28	Diagnostic criteria	Methods of body composition	Prevalence of cachexia (%)
Hugo 2016[28]	France	(n=57) W: 41 M: 16	57.0 ±13.0	3.8 (3.0)	4.4 ± 1.1	Engvall et al[14]	DEXA	18.0
Maghraoui 2015[27]	Morocco	(n=178) W: 147 M: 31	T:54.1± 11.5 W:51.8 ±10.3 M:53.3 ±10.7	8.9 (7.4)	T:4.3± 1.6 W: 4.7± 1.5 M: 4.1±0 1.4	Engvall et al[14]	DEXA	T: 53.9 W:53.7 M: 54.8
Lombard 2013[26]	South Africa	(n=246) W: 204 M: 42	54.7± 13.6		NP	Engvall et al[14]	AM	10.3
Bokhorst 2012[25]	Netherlands	(n=103) W:79 M: 24	*T: 60.0 (26.0-90.0)	*8.0	3.32	Evans et al[11]	BIA; handgrip strength; FAACT; VAS fatigue and pain; CRP; ESR; Hb;	1.0
Elkan 2009[24]	Sweden	(n=80) W: 61 M: 19	*W:60.8 (57.3–64.4) *M: 63.4 (59.8–66.9)	6.0	*W:3.3 (3.0–3.6) *M:2.6 (2.1–3.0)	Engvall et al[14]	DEXA	W: 18.0 M: 21.0
Elkan 2009[23]	Sweden	(n=80) W: 61 M: 19	*W: 60.8 (57.3-64.4) *M:63.4 (59.8-66.9)	6.0	*W:3.3 (3.0 -3.6) *M:2.6 (2.1- 3.0)	FFMI below the 25th percentile and FMI above the 50th percentile.	DEXA	W: 18.0 M: 26.0
Metsios 2009[22]	UK	(n=400) W: 292 M: 108	*+RC:68.3 (64.7–73.0) *-RC: 62.7 (54.0–69.4)	*+RC: 11.0 *-RC: 10.0	RA+RC 4.3 ± 1.8 RA-RC: 4.2 ± 1.4	Engvall et al[14]	BIA	8.5
Engvall 2008[14]	Sweden	(n=60) W: 50 M 10	*W:66.0 (63.0–69.0) *M: 60.0 (51.0–70.0)	*W:13.0 *M:16.0	*W:5.7 (5.3–6.1) *M: 4.6 (3.7–5.5)	Engvall et al[14]	DEXA	38.0

*Median; ±standard deviation; Engvall et al[14] diagnostic criteria, FFMI below the 10th percentile and FMI above the 25th percentile; DAS28: 28-joint disease activity score; T: total; W: women; M: men; +RC: patients with rheumatoid arthritis and rheumatoid cachexia; −RC: patients with rheumatoid arthritis without rheumatoid cachexia; NP: not published; FFMI: fat-free mass index; FMI: fat mass index; AM: anthropometric measurements; FAACT: the Functional Assessment of Anorexia/Cachexia Therapy questionnaire; VAS: visual analogue scale; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; DEXA: total-body dual-energy X-ray absorptiometry; BIA: bioelectrical impedance analysis.

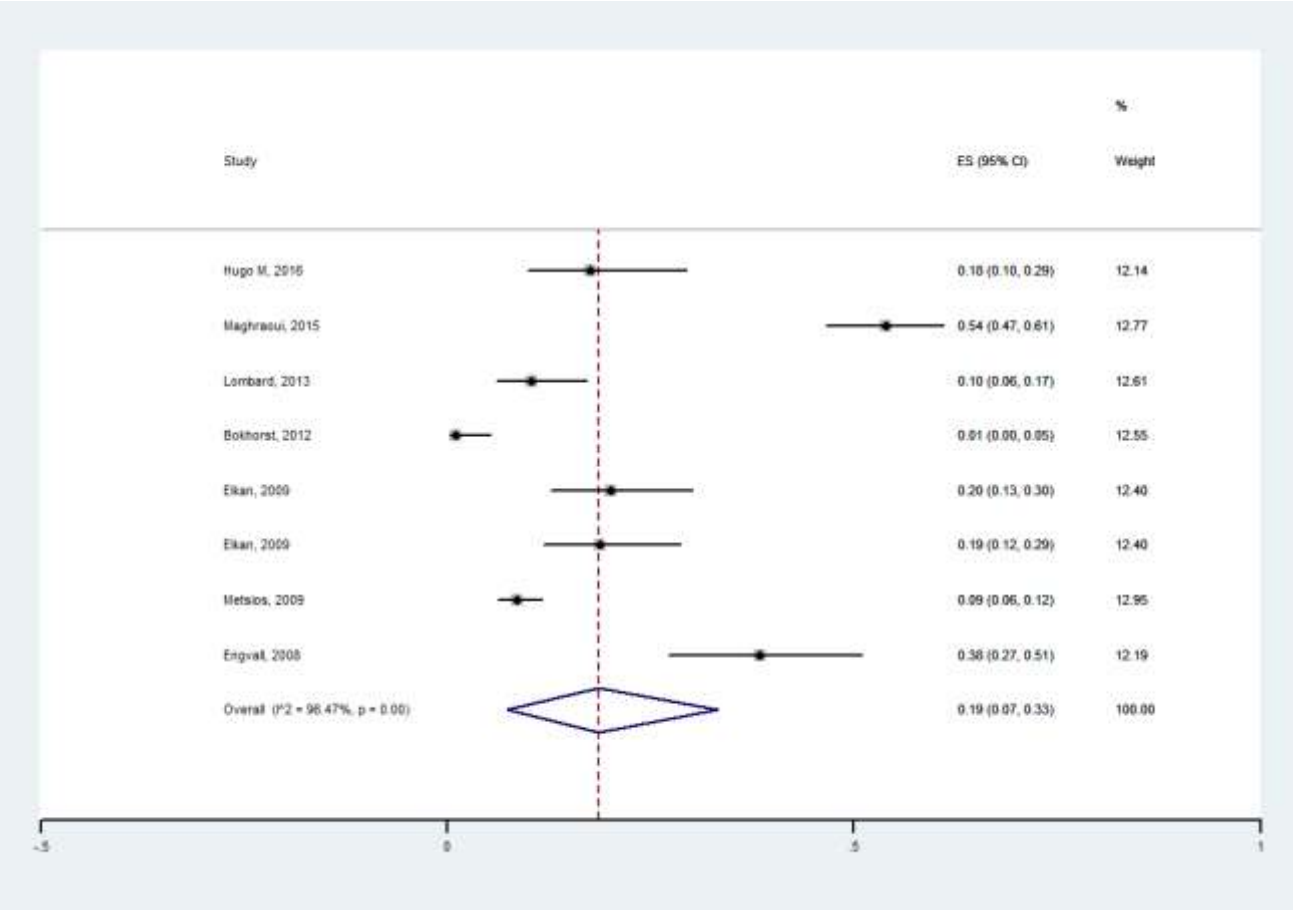


Figure 2. Forest plot of the prevalence of rheumatoid cachexia using body composition (assessed by dual-energy X-ray absorptiometry, bioelectrical impedance analysis, or anthropometric measurements) as a diagnostic criterion; ES, estimated; I^2, heterogeneity among studies.

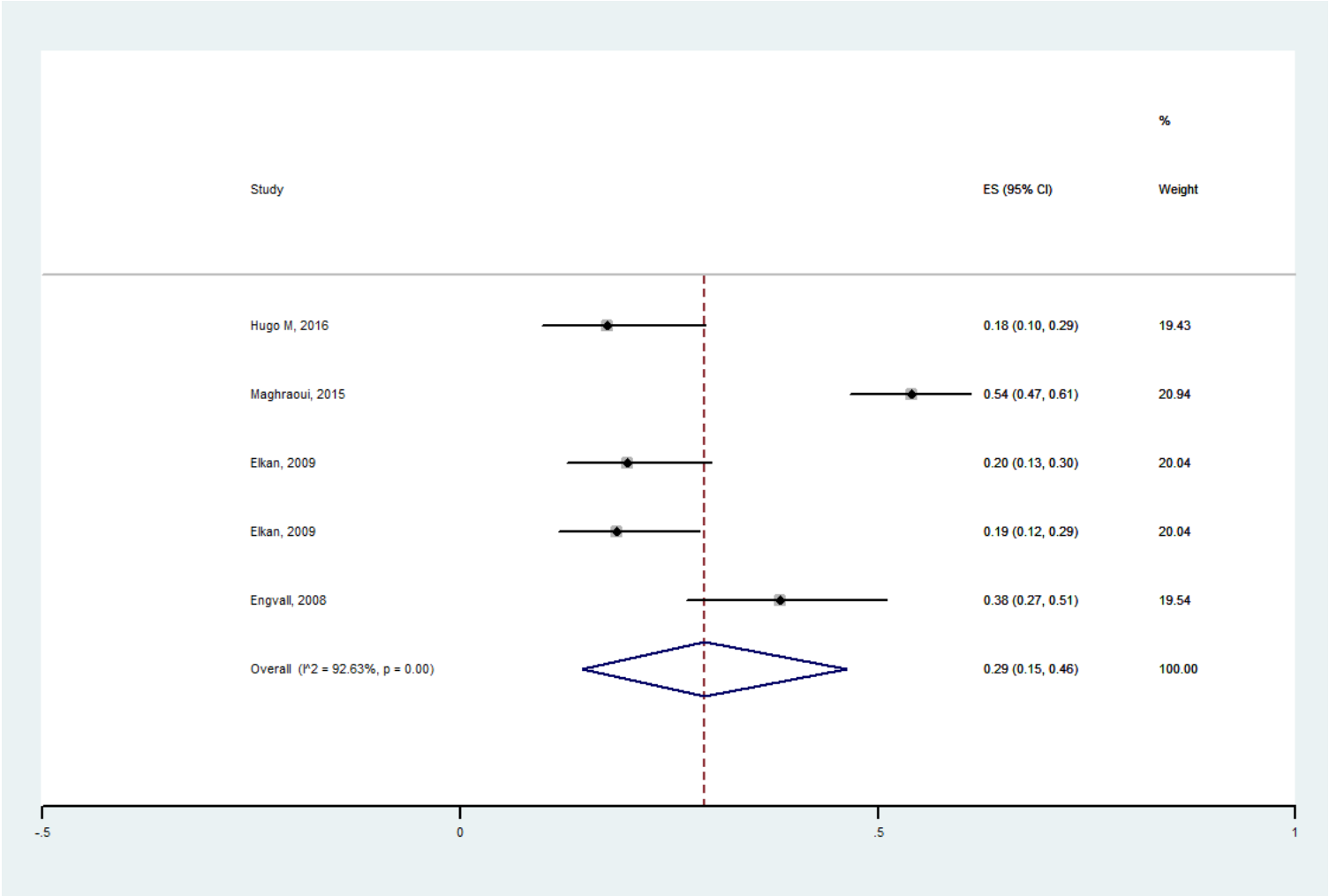


Figure 3. Forest plot of the prevalence of rheumatoid cachexia using dual-energy X-ray absorptiometry (DEXA). ES, estimated; I^2, heterogeneity among studies.

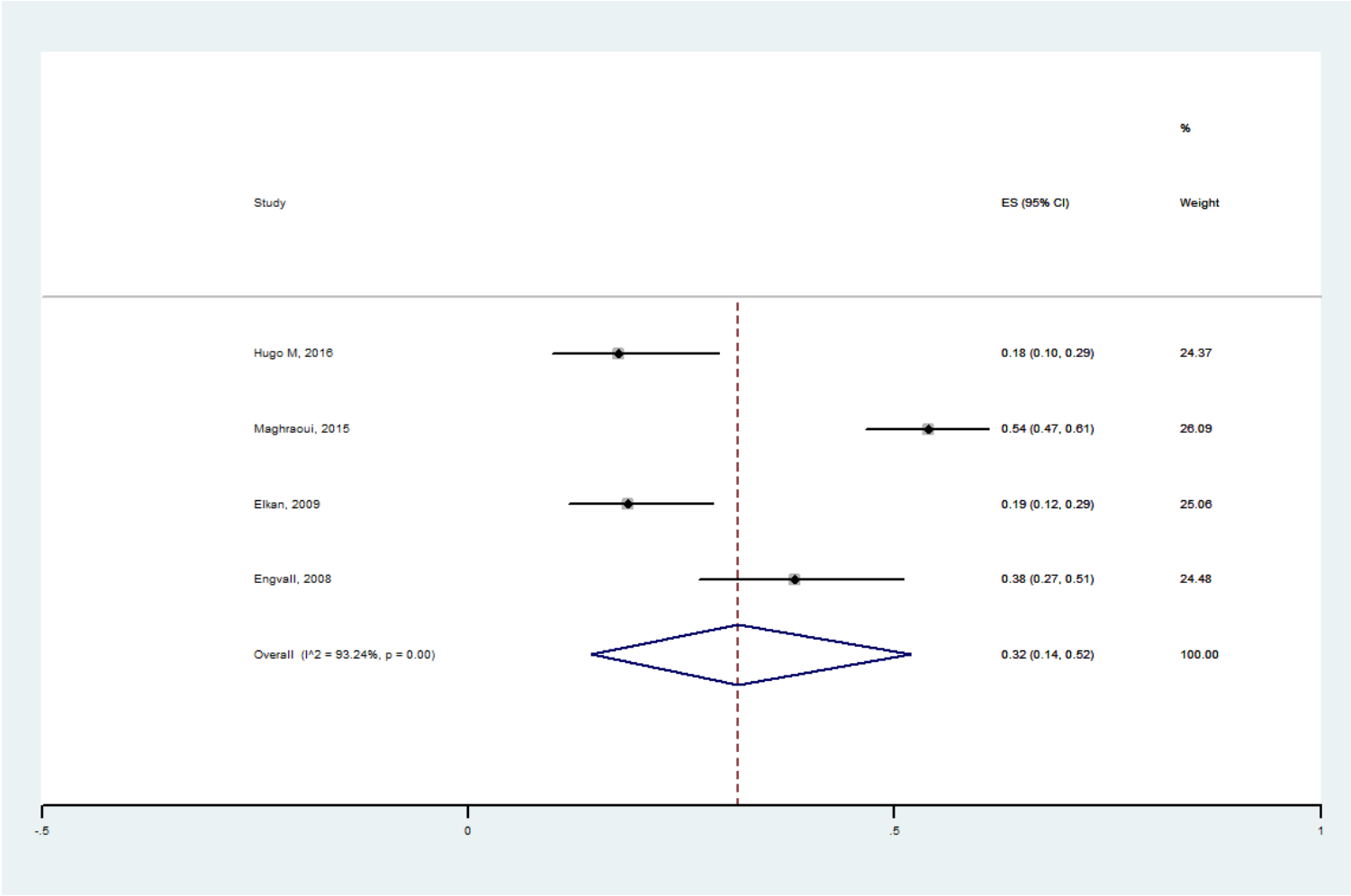


Figure 4. Forest plot of the prevalence of rheumatoid cachexia using dual-energy X-ray absorptiometry (DEXA) and fat-free mass index (FFMI) below the 10th percentile and fat mass index (FMI) above the 25th percentile as diagnostic criteria. ES, estimated; I^2, heterogeneity among studies.

Methodological quality of the studies

The methodological quality of included studies is described in Table 2. Most studies were rated as having moderate quality.

Table 2. Description of quality assessment using the Newcastle-Ottawa Scale (NOS)

First author name	Country	Selection (1-5 stars)	Comparability (1-2 stars)	Outcome (0-3 stars)	Overall NOS (1-10 stars)
Hugo et al[28]	France	**	*	**	5
Maghraoui et al[27]	Morocco	**	*	**	5
Lombard et al[26]	South Africa	****	*	**	7
Bokhorst et al[25]	Netherlands	**	*		3
Elkan et al[24]	Sweden	**	*	**	5
Elkan et al[23]	Sweden	**	*	**	5
Metsios et al[22]	UK	**	*	***	6
Engvall et al [14]	Sweden	**	*	**	5

DISCUSSION

RC is a term used to characterize adverse changes in body composition that involve reduction in FFM and maintenance or increase in FM in patients with RA. These changes may be related to pro-inflammatory cytokine-induced hypermetabolism [13-15]. To our knowledge, this is the first systematic review with meta-analysis to estimate the prevalence of RC in patients with RA. Of the eight articles included in our study: seven studies used diagnostic criteria developed specifically for RC—six used the criteria proposed by Engvall et al [14] and one used the criteria proposed by Elkan et al [23], while one study used the criteria for classic cachexia proposed by Evans et al [11].

The estimated RC prevalence was 19% (95% CI 07-33%) . However, estimated prevalence varied when studies with different methods of body composition assessment or different cutoff points were included in the analysis. In the analysis using specific diagnostic criteria for RC and DEXA, the estimated prevalence of RC was 29%. Nevertheless, in the analysis using specific criteria for RC, DEXA and the cutoff points proposed by Engvall et al [14] (i.e., FFMI below the 10th percentile and FMI above the 25th percentile), the estimated prevalence of RC was 32% (95% CI 14-52%). Therefore, we can state that RC is influenced by the method of body composition assessment and criteria used for diagnosis.

Body composition analysis refers to the quantification of the main structural components of the human body, divided into specific tissues that compose the total body mass [29,30]. Methods of body composition assessment such as DEXA, BIA, and anthropometric measurements have been used in the clinical and research settings. Using BIA, Bokhorst et al [25] found a very low prevalence of RC (1%). Metsios et al [22], also using BIA, found a prevalence of RC of 8.5%. Elkan et al [24] compared BIA and DEXA and found good agreement between the two methods, but BIA showed higher lean mass values and lower FM values. Although BIA has lower cost, greater ease of use, and higher measurement speed, the use of this technique requires that the person undergo a set of previous procedures, without which there may be loss of information quality obtained from FM when compared to DEXA.

In addition to these precautions, equipment characteristics and calibration, body position, individual hydration level and food intake, ambient and cutaneous temperature, use of heavier garments and metal parts may have some influence on the quality of measurements [31,32]. Using anthropometric measurements to assess body composition in patients with RA, Lombard et al [26] found a prevalence of RC of 10.3%. Anthropometric measurement is considered a double indirect method of body composition assessment, and the instruments used, the evaluator's ability, intra and inter-rater errors, individual factors (hydration level, physical exercise, menstrual cycle), and the choice of the anthropometric prediction equation, among other factors, may be a source of error [33-36].

Using DEXA as the method of body composition assessment in patients with RA, Hugo et al [28] found an RC prevalence of 18%, while Maghraoui et al [27] found a prevalence of 53.9%. A number of techniques are being used to assess body composition as water dilution,

anthropometry, DEXA, analysis of computerized tomography and magnetic resonance imaging, and BIA [37]. However, DEXA represents a reliable alternative method, non-invasive , improved feasibility, lower cost, minimal radiation exposure, high accuracy, sensitive and reproducibility for measuring FM and FFM [38,39]. In addition, DEXA is a clinically accessible method that is widely used in bone mineral density measurement for the evaluation of osteoporosis; therefore, it is also suitable for the analysis of body composition.

RC prevalence also varied according to the criteria used for diagnosis, since the diagnostic criteria for RC are not well established. Engvall et al [14] and Elkan et a [23] proposed a RC diagnostic criteria that include changes in FFM and FM. Engvall et al [14] used data from a Swiss population sample of healthy adults (2986 males, 2649 females) to found body composition index that determine RC. Therefore RC was classified as FFMI below the 10th percentile and FMI below the 25th percentile. Using these cutoff points, they found an RC prevalence of 38%. Other studies conducted using the same diagnostic criteria (and cutoff points) found a RC prevalence ranged from 8.5 to 53.9%.

Elkan et al [23] proposed a variation in the same parameters but different cutoff point and the same Swiss population database used by Engvall et al [14] for RC in order to test the association of RC with dyslipidemia and risk of cardiovascular disease. Patients with RA were classified as having RC if they had FFMI below the 25th percentile and FMI above the 50th percentile [14]. Using these cutoff points, they found an RC prevalence of 21% for women and 26% for men. Despite the difference between the RC criteria proposed by Engvall et al [14] and by Elkan et al [23], no apparently difference was observed between prevalence rates.

Evans et al [11], however, proposed a diagnosis of cachexia to be used in several diseases, including RA. Based on these criteria, Bokhorst et al [25] found a prevalence of RC of 1%. Physical inactivity [40] and treatment effects [41-43], due to the effective reversal of the systemic inflammatory process, seem to affect the gain or maintenance of body weight in patients with RA. Therefore, patients with controlled RA do not lose body weight and, for this reason, the prevalence of RC using the diagnostic criteria proposed by Evans et al [11] is lower than that reported in the studies that used the diagnostic criteria proposed by Engvall et al [14] or by Elkan et al [23,24].

In fact, no study evaluated the impact of RC on patient outcomes, and no study prospectively validated these criteria. To define the best criterion, such studies are required.

Despite the lack of body weight loss, patients with RA lose muscle mass compared with healthy individuals. Loss of muscle mass is commonly evaluated in classic cachexia, RC, and sarcopenia; therefore, these syndromes are often confused with one another.

Using loss of muscle mass as a diagnostic criterion for sarcopenia in patients with RA, studies have reported prevalence rates of sarcopenic patients ranging from 11.0 to 57.1%. However, studies that evaluated only loss of muscle mass were not included in our systematic review with meta-analysis, since the objective was to specifically evaluate RC according to currently used RC diagnostic criteria. Considering that patients with RA have a decrease in lean mass, maintenance or increase in adipose tissue, and changes in functionality, Weber et al

[44,45] proposed a new parameter of adiposity-adjusted muscle mass ($ALMI_{FMI}$). This parameter was defined as appendicular lean mass divided by height squared adjusted for age and body fat (adjZ-score), and low lean mass was defined as adjZ-score <-1.0, leading to stronger positive associations with functional results compared to unadjusted estimates in patients with RA [44,45]. Thus, it is suggested that this new parameter be used in future sarcopenia and cachexia studies of patients with RA.

The systemic inflammatory process of RA has been associated with altered body composition and RC [14]. Elkan et al assessed patients with mild to moderate disease activity and found an RC prevalence of 18.0% [23,24] for women and 21.0 [24]-26.0% [22] for men. Conversely, studies evaluating patients with moderate to high disease activity found an RC prevalence of 18-53.9% [14,22,27,28]. In our meta-analysis, no association between disease activity and RC was demonstrated, probably because most patients had moderate to high disease activity (DAS28 between 3.1 and 5.2) and because all studies had a cross-sectional design, thereby preventing the evaluation of changes in body composition and disease activity over time.

Regardless of whether there is agreement between the diagnostic criteria and methods used for body composition assessment, there is common agreement that RC affects the clinical outcome of patients. Patients with RA have increased IL-6 and TNF within the muscle. These muscle inflammatory markers correlate with physical inactivity and disability [46]. Engvall et al [14] demonstrated that patients with RA who had RC and high disease activity had lower physical activity and IGF-1 levels. In addition to muscle alterations, patients with RA also have endothelial dysfunction and increased risk of atherosclerosis and cardiovascular disease [47-49]. However, the effects of RC on the risk of cardiovascular disease are still controversial [50]. Elkan et al [23], in patients with RA who had RC and moderate disease activity, found high levels of total cholesterol and LDL, low levels of IgM against phosphorylcholine (anti-PC IgM), and high frequency of hypertension. However, in patients with RA and moderate RC, disease activity does not appear to be associated with worse cardiovascular disease profile [22] or metabolic syndrome [28]. Impaired bone metabolism may also be present, since patients with RA and RC have lower hip bone mineral density than patients without RC [27]. Considering that RC affects the clinical outcome of patients, longitudinal studies are needed to fill the gaps in the literature regarding the effects of RC on patients with RA.

The main limitation of this study is the small number of RC studies included, making meaningful meta-analysis difficult. In conclusion, the results of this systematic review with meta-analysis indicate that the estimated prevalence of RC ranges from 19 to 32%, and that there is variability in the prevalence rates according to the diagnostic criteria used for RC. Therefore, there is a need for greater standardization of terms such as RC, cachexia, and sarcopenia, as well as for further prospective studies aiming to clarify the impact of this comorbidity on clinical outcomes.

ACKNOWLEDGEMENT

The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015 [51]. We thank the Coordination for the Improvement of Higher Level Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES) institution and the Foundation for Research Support of the Rio Grande do Sul State (Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul - FAPERGS) for granting scholarships to the students that helped develop this study. Also, we thank the Service of Rheumatology and Service of Biostatistics of HCPA by financial and scientific support. This work was supported by the Research and Events Incentive Fund (Fundo de Incentivo à Pesquisa e Eventos - FIPE) of HCPA and by the National Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq).

CONFLICT OF INTEREST STATEMENT/S

Rafaela CE Santo, Kevin Z Fernandes, Priscila S Lora, Lidiane I Filippin, and Ricardo M Xavier declare that they have no conflict of interest.

REFERENCES

1. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001; 358: 903-11.
2. da Mota LM, Cruz BA, Brenol CV, Pereira IA, Fronza LS, Bertolo MB, et al. 2011 Consensus of the Brazilian Society of Rheumatology for diagnosis and early assessment of rheumatoid arthritis. Rev Bras Reumatol 2011;51:199-219.
3. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2016;68:1-26.
4. Roubenoff R, Rall LC. Humoral mediation of changing body composition during aging and chronic inflammation. Nutr Rev 1993;51:1-11.
5. Roubenoff R, Roubenoff RA, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest 1994;93:2379-86.
6. Westhovens R, Nijs J, Taelman V, Dequeker J. Body composition in rheumatoid arthritis. Br J Rheumatol. 1997;36:444-8.
7. Walsmith J, Roubenoff R. Cachexia in rheumatoid arthritis. Int J Cardiol. 2002;85:89-99.
8. Rall LC, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. Rheumatology (Oxford). 2004 ;43:1219-23.
9. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412-23.
10. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, et al. Age Ageing 2014;43:748-59.
11. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr 2008;27:793-9.
12. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics".Clin Nutr 2010; 29: 154–159.
13. Roubenoff R1, Roubenoff RA, Ward LM, Holland SM, Hellmann DB. Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. J Rheumatol 1992;**19**:1505-10.
14. Engvall IL, Elkan AC, Tengstrand B, Cederholm T, Brismar K, Hafstrom I. Cachexia in rheumatoid arthritis is associated with inflammatory activity, physical disability, and low bioavailable insulin-like growth factor. Scand J Rheumatol 2008;**37**:321-8.
15. Summers GD1, Deighton CM, Rennie MJ, Booth AH. Rheumatoid cachexia: A clinical perspective. Rheumatology (Oxford) 2008;**47**:1124-31.
16. Rajbhandary R, Khezri A, Panush RS. Rheumatoid cachexia: what is it and why is it important? J Rheumatol 2011;**38**:406-8

17. Lemmey AB. Rheumatoid cachexia: the undiagnosed, untreated key to restoring physical function in rheumatoid arthritis patients? Rheumatology (Oxford) 2016;**55**:1149-50.
18. Masuko K.Rheumatoid cachexia revisited: a metabolic co-morbidity in rheumatoid arthritis. Front Nutr 2014;**1**:20.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, et al. *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS 2009;6(7): e1000097.
20. Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, et al. Panethnic Differences in Blood Pressure in Europe: A Systematic Review and Meta-Analysis. PLoS One 2016; **25**:e0147601
21. Toledano E1, Candelas G, Rosales Z, Martínez Prada C, León L, Abásolo L, et al. A meta-analysis of mortality in rheumatic diseases. Reumatol Clin 2012;**8**:334-41.
22. Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, Sandoo A, Toms TE, Nevill AM, et al. Rheumatoid cachexia and cardiovascular disease. Clin Exp Rheumatol 2009;**27**:985-8.
23. Elkan AC1, Håkansson N, Frostegård J, Cederholm T, Hafström I. Rheumatoid cachexia is associated with dyslipidemia and low levels of atheroprotective natural antibodies against phosphorylcholine but not with dietary fat in patients with rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther. 2009;**11**:R37.
24. Elkan AC, Engvall IL, Cederholm T, Hafström I. Rheumatoid cachexia, central obesity and malnutrition in patients with low-active rheumatoid arthritis: feasibility of anthropometry, Mini Nutritional Assessment and body composition techniques. Eur J Nutr 2009;**48**:315-22.
25. van Bokhorst-de van der Schueren MA, Konijn NP, Bultink IE, Lems WF, Earthman CP, van Tuyl LH. Relevance of the new pre-cachexia and cachexia definitions for patients with rheumatoid arthritis. Clin Nutr. 2012;**31**:1008-10.
26. Lombard LA1, du Plessis LM, Visser J. Body composition of rheumatoid arthritis patients in the City of Cape Town, South Africa. Clin Rheumatol 2014;**33**:467-76.
27. El Maghraoui A, Sadni S, Rezqi A, Bezza A, Achemlal L, Mounach A. Does Rheumatoid Cachexia Predispose Patients with Rheumatoid Arthritis to Osteoporosis and Vertebral Fractures? J Rheumatol 2015;**42**:1556-62.
28. Hugo M, Mehsen-Cetre N, Pierreisnard A, Schaeverbeke T, Gin H, Rigalleau V. Energy expenditure and nutritional complications of metabolic syndrome and rheumatoid cachexia in rheumatoid arthritis: an observational study using calorimetry and actimetry. Rheumatology (Oxford) 2016;**55**:1202-9.
29. Heymsfield, S. Human body composition 2nd ed. Champaign, Ill. ; Leeds : Human Kinetics, 2005.

30. Petroski, EL. Antropometria: técnicas e padronizações. 5ed. Fontoura;2007.

31. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis--part I: review of principles and methods. Clin Nutr. 2004;23(5):1226-43.
32. Ellis KJ, Bell SJ, Chertow GM, Chumlea WC, Knox TA, Kotler DP, et al. Bioelectrical impedance methods in clinical research: a follow-up to the NIH Technology Assessment Conference. Nutrition 1999;15(11-12):874-80.
33. Conde WL, Oliveira DR, Borges CA, Baraldi LG. Consistência entre medidas antropométricas em inquéritos nacionais. Rev. Saúde Pública 2013;41(1) :69-76.
34. Perini TA, Oliveira GL, Ornellas JS, Oliveira FP. Cálculo do erro técnico de medição em antropometria. Rev Bras Med Esporte 2005;11(1):81-85.
35. Ribeiro G, Lopes A. Análise da Composição corporal: evolução histórica do modelo anatômico de análise tecidual. Rev. Bras. Prescrição e Fisiol. do Exerc 2017;11(68):620-625.
36. Cyrino ES, Okano AH, Glaner MF, Romanzini M, Gobbo LA, Makoski AB, et al. Impact of the use of different skinfold calipers for the analysis of the body composition. Rev. Bras. Med. do Esporte 2003; 9(3):150-153.
37. Tewari N, Awad S, Macdonald IA, Lobo DN.A comparison of three methods to assess body composition, 2018] Nutrition. 2018;47:1-5.
38. Lee SY, Gallagher D.Assessment methods in human body composition. Curr Opin Clin Nutr Metab Care. 2008 Sep;11(5):566-72.
39. Kanellakis S1, Manios Y. Validation of five simple models estimating body fat in white postmenopausal women: use in clinical practice and research. Obesity (Silver Spring). 2012 Jun;20(6):1329-32
40. Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Panoulas VF, Douglas KM, Jamurtas AZ. What predicts obesity in patients with rheumatoid arthritis? An investigation of the interactions between lifestyle and inflammation. Int J Obes (Lond) 2010;34(2):295-301.
41. Tournadre A, Pereira B, Dutheil F, Giraud C, Courteix D, Sapin V, et al. Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. J Cachexia Sarcopenia Muscle 2017;8(4):639-646.
42. Baker JF, Sauer BC, Cannon GW, Teng CC, Michaud K, Ibrahim S, et al. Changes in Body Mass Related to the Initiation of Disease-Modifying Therapies in Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(8):1818-27.
43. Jurgens MS, Jacobs JW, Geenen R, Bossema ER, Bakker MF, Bijlsma JW, et al. Increase of body mass index in a tight controlled methotrexate-based strategy with prednisone in early rheumatoid arthritis: side effect of the prednisone or better control of disease activity? Arthritis Care Res (Hoboken). 2013;65(1):88-93.
44. Weber D, Long J, Leonard MB, Zemel B, Baker JF. Development of Novel Methods to

Define Deficits in Appendicular Lean Mass Relative to Fat Mass. PLoS One. 2016;11(10):e0164385.

45. Baker JF, Giles JT, Weber D, Leonard MB, Zemel BS, Long J, et al. Assessment of muscle mass relative to fat mass and associations with physical functioning in rheumatoid arthritis. Rheumatology (Oxford). 2017; 1;56(6):981-988.
46. Huffman KM, Jessee R, Andonian B, Davis BN, Narowski R, Huebner JL, et al. Molecular alterations in skeletal muscle in rheumatoid arthritis are related to disease activity, physical inactivity, and disability. Arthritis Res Ther. 2017;23;19(1):12.
47. Flierl U, Bauersachs J, Schäfer A. Modulation of platelet and monocyte function by the chemokine fractalkine (CX3 CL1) in cardiovascular disease. Eur J Clin Invest. 2015 ;45(6):624-33.
48. Bergholm R, Leirisalo-Repo M, Vehkavaara S, Mäkimattila S, Taskinen MR, Yki-Järvinen H. Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis. Arterioscler Thromb Vasc Biol. 2002; 1;22(10):1637-41.
49. Berckmans RJ, Nieuwland R, Tak PP, Böing AN, Romijn FP, Kraan MC. Cell-derived microparticles in synovial fluid from inflamed arthritic joints support coagulation exclusively via a factor VII-dependent mechanism. Arthritis Rheum. 2002;46(11):2857-66.
50. Summers GD, Metsios GS, Stavropoulos-Kalinoglou A, Kitas GD. Rheumatoid cachexia and cardiovascular disease. Nat Rev Rheumatol. 2010;6(8):445-51.]
51. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. J Cachexia Sarcopenia Muscle 2015;6: 315-316.

7.2. **ARTIGO 2**: Cachexia and its associated factors in Rheumatoid Arthritis patients: A Cohort study

Cachexia and its associated factors in Rheumatoid Arthritis patients: A Cohort study

Rafaela CE Santo 1,2,3, Jordana MS Silva 1,2,3, Bárbara J Bartikoski 1,2,3, Eduarda C Freitas1,2,3, Ana Laura D Moro 3, Nicole PB Andrade 3, Penélope E Palominos 3, Vanessa Hax 3, Tayane M Fighera 4, Poli Mara Spritzer 4, Rafael MS Chakr 2,3, Joshua F Baker 5, Priscila S Lora 6, Ricardo M Xavier 1,2,3.

1 Hospital de Clínicas de Porto Alegre, Laboratório de Doenças Autoimunes, Porto Alegre, Brazil;
2 Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Porto Alegre, Brazil;
3 Hospital de Clínicas de Porto Alegre, Serviço de Reumatologia, Porto Alegre, Brazil;
4 Hospital de Clínicas de Porto Alegre, Serviço de Endocrinologia, Porto Alegre, Brazil;
5 University of Pennsylvania, Philadelphia, the *United States of America*;
6 Universidade do Vale do Rio dos Sinos, São Leopoldo, Brazil.

Corresponding author: Ricardo M Xavier, e-mail: rxavier10@gmail.com, telephone: +55 51 3359 8837; fax number: +55 51 3359 8340.

Abstract

Background: Rheumatoid arthritis (RA) is an inflammatory disease that leads to altered body composition. The decreased fat-free mass and increased fat mass in RA patients is termed rheumatoid cachexia (RC), while classical cachexia is determined by body weight loss of 5% or more within 12 months added to other features. In RA, there are few data evaluating prevalence, progression and risk factors of cachexia over time. Our aim was to determine the prevalence of cachexia (RC and classical cachexia) in RA patients, and to identify factors associated with cachexia in these patients, at baseline and after one-year of follow-up.

Methods: This is a prospective cohort study. Consecutive RA patients, according to ACR/EULAR 2010 classification criteria, were recruited from a RA clinic of a university hospital and followed for one year. The following assessments were performed at baseline and after one year: disease status (disease activity by DAS28 and drugs), body composition by Dual-energy X-ray absorptiometry, physical function (HAQ-DI, hand grip strength by Jamar dynamometer, gait speed by timed up and go and lower extremity strength by 30s-sit-stand test), fatigue by the Functional Assessment of Chronic Illness Therapy fatigue scale, anorexia by the Functional Assessment of Anorexia/Cachexia Therapy and serum inflammatory markers. Frequency analysis, the pairwise T Student test, McNemar test and GEE analyses were used and statistical significance was considered as $p \leq 0.05$.

Results: Eighty-one RA patients completed the one-year follow-up. Most of the patients were women (88.9%), with mean age of 56.5±7.3 and moderate disease activity (mean DAS28 4.0±1.3). At baseline, 13.3-30.0% of RA patients presented RC, according to the evaluation criteria used, while none of the patients met the classical cachexia criteria. The prevalence of RC or classical cachexia did not change between baseline and 12 months assessments ($p>0.05$). Handgrip strength decreased after 12 months ($p<0.05$). Disease remission was significantly associated with increased body weight and adipose mass after 12 months, higher fat free mass, lower HAQ, higher hand grip strength and low muscle strength of lower limbs ($p<0.05$) compared to patients with disease in activity. Treatment with biologic DMARDs was associated with low BMI, higher fat-free mass and gait speed ($p<0.05$).

Conclusions: In this cohort of established RA patients, RC was frequent, but no classical cachexia was identified. Physical function was found to be limited at baseline, and handgrip strength decreased significantly after 12 months. The observations that function and body composition were affected by remission state and biologic use stresses the importance of adequate control of disease activity at early stages of the disease.

Keywords: Cachexia; Rheumatoid Arthritis; Rheumatoid Cachexia;

Introduction

Rheumatoid arthritis (RA) is an autoimmune, chronic, progressive, inflammatory disease characterized by symmetrical, destructive polyarthritis and is accompanied by systemic manifestations (1,2). RA affects 0.5% to 1% of the population (3,4) and is more frequent in

females than in males (0.35% versus 0.13%) (5). One third of RA patients present comorbidities on the onset of the disease, and during follow-up this number reaches nearly 80% (6). These comorbidities result not only in increased healthcare costs, but also in functional disability, poorer quality of life, and increased mortality for the patients (7).

One comorbidity that often occurs in RA is rheumatoid cachexia (RC), currently characterized by changes in body composition (8–12), such as reduction of fat-free mass (FFM) with increased fat mass (FM), little or no weight loss and maintained body mass index (BMI) (8–12). These modifications are accompanied by altered metabolism, which involves increased energy expenditure and increased protein degradation induced by proinflammatory cytokines (8–12).

There are several diagnostic criteria for RC. The first reported clinical criteria was developed by Engvall et al (13) and classifies RC by fat-free mass index (FFMI) below the 10^{th} and fat mass index (FMI) above 25^{th} percentile, using a Swiss population as reference. Subsequently, Elkan (14) et al proposed a more stringent criteria, characterized by FFMI below the 25^{th} and FMI above 50^{th} percentile using the same population as reference. On the other hand, Evans et al (15) proposed a diagnosis of classical cachexia for diseases in general, including RA. These criteria includes body weight loss of 5% or more within 12 months (or a BMI ≤20 kg/m^2) and at least three of the following factors: decreased muscle strength; fatigue; anorexia; low fat mass index; abnormal biochemistry (increased inflammatory markers [CRP, IL-6], anemia [Hb <12 g/dL], low serum albumin [<3.2 g/dL].

In a systematic review with meta-analysis we found that the RC prevalence in RA patients ranges from 15% to 32% (16), depending of the method of body composition assessment and RC criteria used. None of the studies evaluated the incidence of RC over time.

The impact of RC on the clinical outcomes of RA patients is not well studied. Several authors reported that RC patients show increased serum levels of inflammatory markers (IL-1 β, IL-6, and TNF)(15,17), decreased serum levels of insulin growth factor (IGF-1)(13) and decreased hip bone mineral density(18). Risk of cardiovascular disease or metabolic syndrome on RC patients are still controversial(14,19,20). However, the burden of RC on morbidity and mortality may be difficult to demonstrate because all previous studies had a cross-sectional design. Therefore, prospective studies on body composition and clinical outcomes are needed.

We, therefore, conducted a prospective study in a cohort of patients with established RA to evaluate the long-term impact of cachexia. Here we present the prevalence of cachexia (RC and classical cachexia) and its associated factors in RA patients over one-year of follow-up.

Methods

Study design and patients

This is a prospective cohort study, performed at a tertiary public hospital in Brazil Hospital de Clínicas de Porto Alegre – HCPA) between June 2015 and July 2017. Ninety patients diagnosed with RA according to the American College of Rheumatology (ACR) criteria for RA (21) and aged between 40 and 70 years were enrolled at baseline. The exclusion criteria comprised the presence of dysphagia, illicit drug use and alcohol abuse, severe heart failure (defined as New York Heart Association (NYHA) class III or IV), severe chronic obstructive pulmonary disease, abnormal hepatic function, uncontrolled diabetes (fasting glucose >140 mg/dL or random glucose levels >200 mg/dL), thyroid dysfunction (hypothyroidism or hyperthyroidism) and severe kidney disease (glomerular filtration rate <15 ml/min). Also, patients with malignant disease, deformities in the lower limbs and surgical history in the previous year were excluded. This study was approved by the Institutional Review Board (IRB) and is registered under the number 15-0297. To decrease potential sources of bias, the collection of data was performed by the same group of health professionals throughout the study.

Data Collection

Patients were evaluated in two time points: at baseline and after 12 months. Age, disease duration (years), anti-CCP, disease activity and pharmacological treatment used by patients were assessed in patient medical records. The RC determination included the evaluation of fat free mass index (FFMI) and fat mass index (FMI). The presence of classical cachexia was assessed by the analysis of body weight, hand grip strength, fatigue, anorexia, FFMI, inflammatory markers (CRP, IL-6), hemoglobin and serum albumin. Additionally, other factors related to cachexia, such as low fat-adjusted lean for age, physical function, blood glucose and lipid profile, were analyzed.

Disease activity. The disease activity of the patients was measured by Disease Activity Score-28 (DAS-28), which includes count of swollen and tender joints (out of the 28), the erythrocyte sedimentation rate (ESR) and global disease activity measured on a visual analogue scale (VAS) (22). According to DAS-28 categories, the disease activity is classified as remission (≤2.6), low (2.6>DAS≤3.2), moderate (3.2>DAS≤5.1) and high (DAS>5.1).

Body composition. Body composition was evaluated by Dual-energy X-ray absorptiometry (DXA; Prodigy Primo System GE Medical Systems Lunar). Whole-body DXA was performed on all participants to estimate fat-free mass, total fat mass and appendicular lean mass. Fat free mass index (FFMI) and fat mass index (FMI) were determined by dividing the respective estimate by height-squared (23,24). The patients were categorized as rheumatoid cachectic when FFMI was below the 10^{th} percentile and FMI above the 25^{th} percentile(13) or when FFMI was below the 25^{th} percentile and FMI above the 50^{th} percentile(14).

Body weight. Body weight/unintentional weight loss was determined by anthropometric scale with a resolution of 100g (Filizola S.A. Pesagem e Automação, São Paulo, Brazil). Body mass index (BMI) was calculated from the weight and height values (weight divided by the square of the height; Kg/m²) and categorized as low (<18,5Kg/m²), normal (18,5-24,9Kg/m²), high (25-29,9Kg/m²) or very high (≥30Kg/m²) according to the gender-independent World Health Organization (WHO) categories (25).

Hand grip strength. Hand grip strength was determined using a hand-held dynamometer (Jamar Hydraulic Hand Dynamometer, Preston/USA) with the patient in the seated position with elbow flexed at 90°, following the recommendations of American Society of Hand Therapists (ASHT). The patient was instructed to squeeze the handle as hard as possible for five seconds, to detect the maximal isometric voluntary contractions (MIVC) of each hand. The measurement was repeated after a recovery period of 30 seconds, and the maximum value of three isometric contractions was used in the analyses. Values of hand grip strength <30 kg for men and <20 kg for women are considered as low muscle strength (26).

Fatigue. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F, validated to Portuguese language) questionnaire. FACIT-F comprises a set of 40 questions is divided into 5 subsets: physical, social, emotional, and functional well-being and additional concerns. Each of these subsets consists of a few questions with responses ranging from 0 to 4, meaning ‘‘not at all’’ to ‘‘very much’’. The sum score ranges from 0 to 52, whereby a lower score indicates more fatigue. Scores ≤20 characterize fatigue (27).

Anorexia. Anorexia was measured using the anorexia/cachexia section of Functional Assessment of Anorexia/Cachexia Therapy (FACCT, validated to Portuguese language) questionnaire. FACCT were filled out based on the patients’ experience regarding their appetite during the last 7 days. The 12 items of the questionnaire were scored on a five-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much). The sum score ranges from 0 to 48, whereby a lower score indicates less appetite. Anorexia was defined as a FAACT score ≤24 (28).

Low fat free mass index. FFMI was measured by DXA (kg/m^2). Lean tissue depletion was considered as values <5.45 kg/m^2 for women and <7.25 kg/m^2 for men (15).

Blood analysis. Fasting and fresh blood samples of each subject were collected at baseline and after 12 months to measure acute-phase reactants (CRP and ESR), hemoglobin, and albumin. All analyses were performed by the Clinical Pathology Division of the HCPA. Additionally, serum blood samples were frozen and stored for the evaluation of the pro-inflammatory cytokine interleukin-6 (IL-6) by Enzyme-Linked Immunosorbent Assay (ELISA; BioLegend, Inc.).

Low fat-adjusted lean for age. To determine low fat-adjusted lean for age we used body composition parameters proposed by Weber et al (29). Appendicular lean mass index (ALMI) and FMI were used to generate sex-, and race-specific standard deviation scores (Z-Scores). Adiposity-adjusted ALMI Z-scores ($ALMI_{FMI}$) were generated by utilizing the residuals from the regression of ALMI Z-score on FMI Z-score within age, sex and race categories. Low fat-adjusted lean for age was defined as $ALMI_{FMI}$ Z-score ≤-1 (29,30).

Gait speed. Gait speed was assessed by Timed Up and Go (TUG) test (31,32). For TUG, patients were seated on a chair and performed 'stand-up and go', moving 3 meters and turning back to the chair to sit down again at a comfortable speed. The more time needed to complete the test, the greater the restriction of mobility and the higher the risk of falling. Low gate speed was considered as <0.8 m/s.

Muscle strength of the lower limbs. Muscle strength of the lower limbs was evaluated by 30second-sit-stand test (32,33). For this test, patients remained with both arms crossed against the chest, starting from the seated position and standing up (legs straight) and sitting down (full weight on the chair). Then, the number of stands a patient could complete in 30 seconds was registered. Low muscle strength was considered as <12 for women and <14 for men.

Physical disability. Physical disability was assessed by Health Assessment Questionnaire-Disability Index (HAQ-DI) (34). Briefly, eight categories are assessed, including dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. For each of these categories, patients report the amount of difficulty they have in performing two or three specific activities and whether they require assistance or the use of assistive devices to perform that activity.

Glucose and lipid profile. Glucose and lipid profile analyses were performed by the Clinical Pathology Division of the HCPA. Lipid profile [total cholesterol (TC), high-density cholesterol (HDL), low-density cholesterol (LDL), and triglyceride (TG)] were measured.

Statistical analysis

The sample size was calculated based on the study "Rheumatoid Cachexia revisited: a metabolic co-morbidity in Rheumatoid arthritis" (35), which demonstrated a RC prevalence of 38% in RA patients. Assuming an error of 10% and a significance level of 5%, a sample size of 90 RA patients was estimated for the study. The Kolmogorov–Smirnov method was used as the normality test. Results are expressed as mean ± standard deviation (SD), median (and interquartile range) and number (percentages, %) as appropriate. The pairwise T Student test

was used to compare variables between baseline and 12 months assessments. McNemar's test was used on paired nominal data. Pearson correlation coefficients were explored. The Generalized estimating equation (GEE) was performed using linear or gamma model when appropriate. We analyzed gender, time, disease status (disease remission characterized by DAS28 ≤ 2.6 and not remission by DAS28 > 2.6) and biologics treatment (patients treated with biologic and patients treated with non-biologic) on body composition parameters and physical function parameters. Estimated mean and standard error (SE) were used when GEE analysis was performed. The significance level to all analysis was set at $p \leq 0.05$. Statistical analyses were performed with IBM SPSS 18.0 Statistics for Windows.

Results

Patients Characteristics

Of the 90 RA patients recruited, 81 completed the one-year follow-up. Of the nine dropouts, two patients died, five patients withdrew the consent and two patients moved out of the study region or contact was not possible (figure 1). One of the patients died of stroke and was diagnosed with RC, according to the criteria of Engvall (13) and Elkan (14), but was not diagnosed with classical cachexia (15), at baseline. The cause of death of the other patient was not identified and this patient was not diagnosed with either RC or classical cachexia at baseline.

At baseline, mean±SD age of patients was 56.5±7.3 years and the median of disease duration was 8 (3-18) years. The majority of the patients were women (78/90; 86.7%). Of the 90 patients included, 45 patients had anti-CCP evaluation and 34 (75.5%) were positive. The mean±SD DAS28 score was 3.7±1.4. Thirty percent (27/90) of the RA patients were treated with biologic disease modifying antirheumatic drugs (bDMARDs), 93.3% (84/90) were using conventional synthetic DMARD (csDMARD) and 50% (45/90) were using glucocorticoids. After 12 months, the use of bDMARD, csDMARD and glucocorticoids did not change (no significance (NS) $p>0.05$), however, mean DAS28 increased over time (mean and SD of 4.0±1.3; $p<0.05$). More details about demographic and clinical characteristics data are described in table 1.

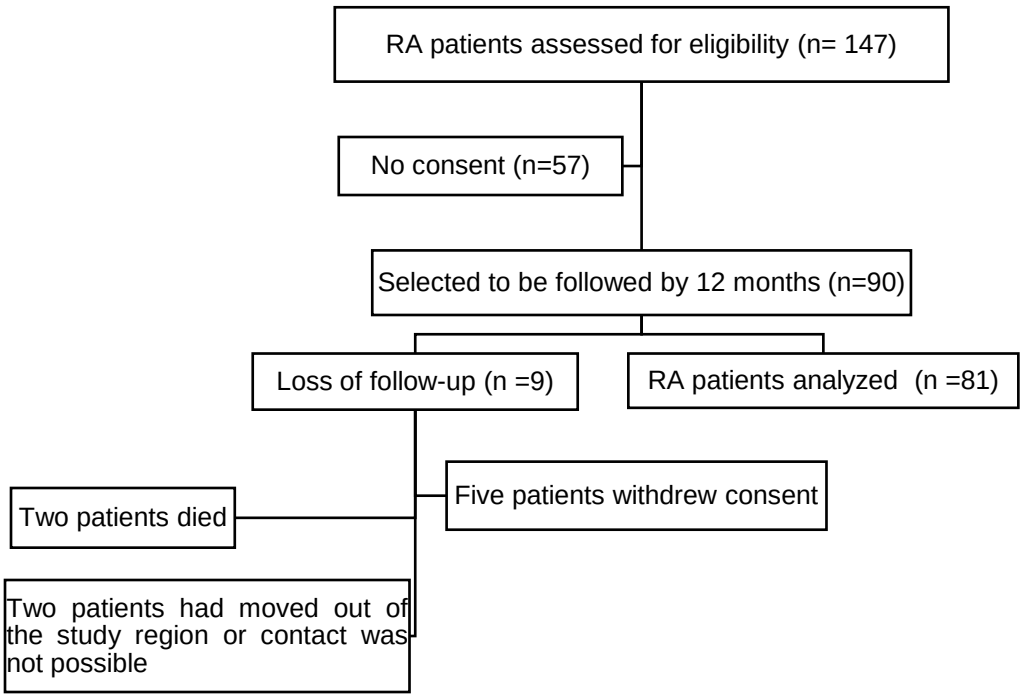


Figure 1 – The flow diagram of the study population

Table 1 - Demographic and clinical characteristics of RA patients at the baseline visit

	Baseline (n=90)	At 12 months (n=81)	p
Age (years), (mean ± SD)	56.5 ± 7.3		
Disease duration (years),(median (IQR)	8 (3-18)		
Women (n,%)	78 (86.7)	72 (88.9)	
Men (n,%)	12 (13.3)	9 (11.1)	
Caucasian (n,%)	62 (68.9)		
Current smoker (n,%)	18 (20.0)		
Rheumatoid factor positive (n,%)	77 (85.6)		
Anti-CCP-positive, n (%)	34/45 (75.5)		
Presence of erosion (n,%)	64 (71.1)		
Disease Activity			
DAS-28 (mean ± SD)	3.7 ± 1.4	4.0 ± 1.3	0.045*
Remission (n,%)	18 (20.0)	15 (16.7)	NS**
Low (n,%)	13 (14.4)	8 (8.9)	NS**
Moderate (n,%)	35 (38.9)	37 (41.1)	NS**
High (n,%)	14 (15.6)	21 (23.3)	NS**
ESR, (median (IQR))	22.5 (13.7 – 35.2)	31.0 (19.2 – 42.0)	0.000*
$Pain_{VAS,}$ (mean ± SD)	4.0 (3.0)	3.6 (2.8)	NS*
Medication			
bDMARDs (n,%)	27 (30.0)	29 (32.2)	NS**
csDMARDs (n,%)	84 (93.3)	76 (84.4)	NS**
Glucocorticoid (n,%)	45 (50.0)	42 (46.7)	NS**

*The pairwise T Student Test; ** McNemar Test; NS, no significance; csDMARDs (conventional synthetic disease modifying antirheumatic drugs): Methotrexate, Leflunomide, Hydroxychloroquine and Sulfasalazine; bDMARDs (disease modifying antirheumatic drugs): Adalimumab, Etanercept, Infliximab, Certolizumab, Golimumab, Rituximab, Tocilizumab, Abatacept.

Prevalence of rheumatoid cachexia

The prevalence of RC at baseline and after 12 months is illustrated in figure 2. At baseline and after 12 months, 12 patients were classified as RC by diagnostic criteria of Engvall et al (13). Using the diagnostic criteria defined by Elkan et al (14), 27 patients at baseline and 22 patients after 12 months were classified as rheumatoid cachectic. There was no significant difference in RC prevalence between baseline and 12 months by both diagnostic criteria (NS). At baseline, we did not find significant associations between DAS28 and RC parameters (NS). Therefore,

we performed GEE analysis to assess the effects of disease activity status and treatment with bDMARDs on RC parameters (table 2 and 3). Women in remission showed higher FFMI compared to women in non-remission ($p<0.05$; table 2). In addition, men treated with bDMARDs showed an increase in FFMI after 12 months ($p<0.001$; table 3). Patients in remission increased FMI after one-year follow-up ($p<0.001$; table 2). Treatment with bDMARDs was not related to changes in FMI (NS; table 3).

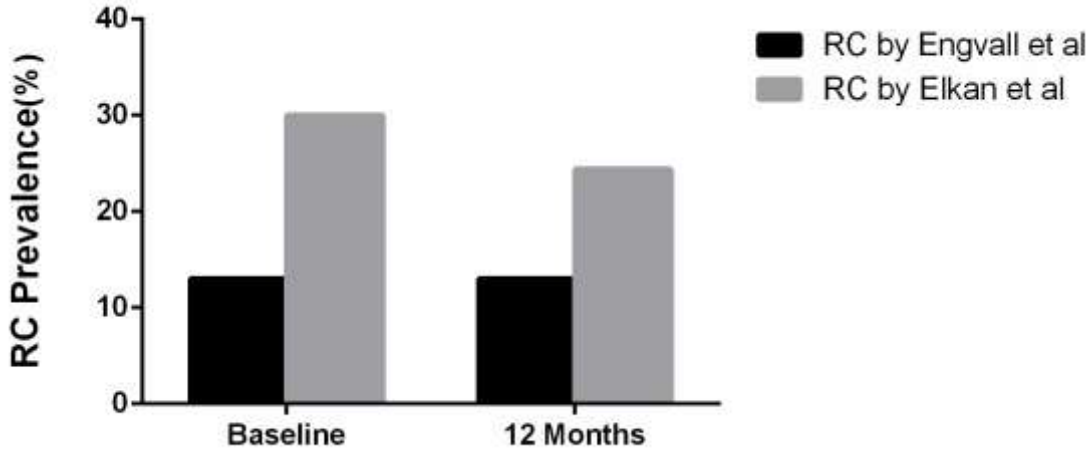


Figure 2. RC prevalence using the diagnostic criteria proposed by Engvall et al and Elkan et al.

Prevalence of classical cachexia

None of the patients presented classical cachexia defined by the criteria proposed by Evans et al (15). Nevertheless, five RA patients (5.5%) presented BMI <20.0 kg/m^2 at baseline. At baseline, mean±SD of body weight was 68.8±14.4 kg for women and 76.3±13.8 kg for men. Regarding BMI, mean±SD was 27.6±5.2 kg/m^2 for women and 25.8±4.3 kg/m^2 for men. After 12 months, mean±SD of body weight was 69.4±14.3 kg for women and 73.1±11.9 kg for men, while mean±SD of BMI was 28.2±5.2 kg/m^2 for women and 24.9±3.3 kg/m^2 for men. Women showed higher BMI than men ($p<0.05$) in both times, and increased body weight and BMI after one-year follow-up ($p<0.001$). Disease activity status and bDMARDs use were not related to body weight changes (NS, table 2 and 3), however, patients treated with bDMARDs showed increased BMI after 12 months ($p<0.001$; table 3).

According to handgrip muscle strength analysis, fifty-nine women (75.6%) had low muscle strength (<20kg) and 8 men (66.7%) had low muscle strength (<30kg) at baseline. After 12 months, 69 women (95.8%) and 6 men (66.7%) had low muscle strength. Mean muscle

strength decreased after 12 months in both genders (p<0.001 for women and p<0.05 for men). Patients in remission had higher muscle strength compared to non-remission patients (p<0.001). Treatment with bDMARDs was not related to muscle strength changes (NS) (figure 3).

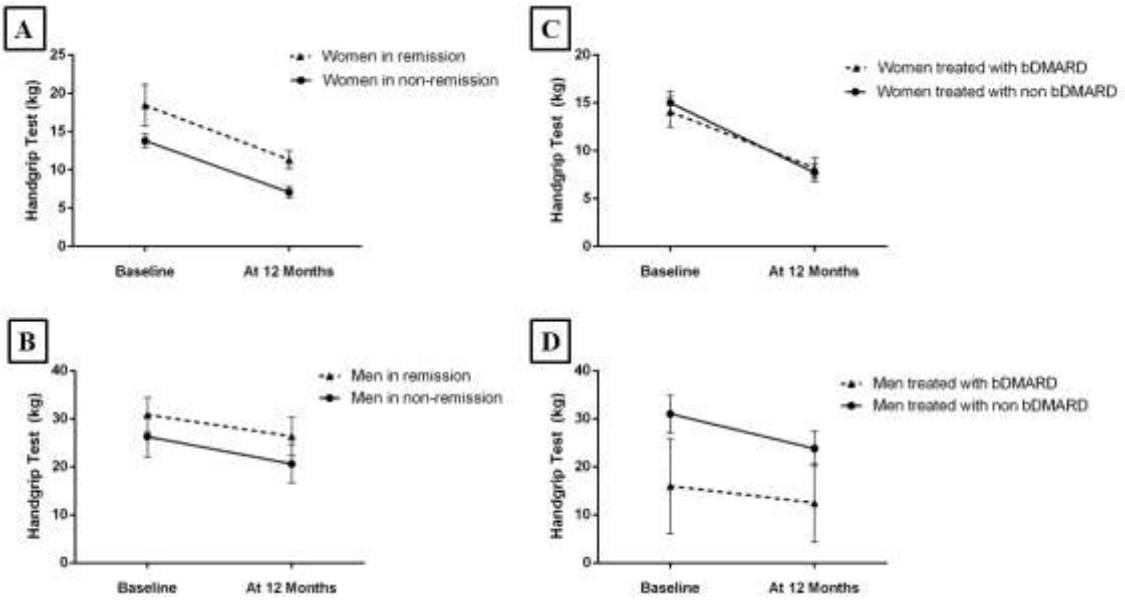


Figure 3. A) Mean±SD of handgrip muscle strength of women in remission and women in non-remission at baseline and after 12 months. b) Mean±SD of handgrip muscle strength of men in remission and men in non-remission at baseline and after12 months. C) Mean±SD of handgrip muscle strength of women treated with bDMARDs and women non-treated with bDMARDs at baseline and after 12 months. D) Mean±SD of handgrip muscle strength of men treated with bDMARDs and men non-treated with bDMARDs at baseline and after 12 months. Remission = 18 RA patients at baseline and 15 RA patients at 12 months; Non- remission = 72 RA patients at baseline and 66 RA patients at 12 months; Patients treated with bDMARDs = 27 RA patients at baseline and 29 RA patients at 12 months; Patients non-treated with bDMARDs = 63 RA patients at baseline and 52 RA patients at 12 months.

Thirteen patients (14.3%) showed severe fatigue (FACIT score≤20) at baseline and seven patients (8.6%) showed severe fatigue after 12 months. The mean±SE of FACIT-F was 36.5±59.4 at baseline and 39.2±63.6 after 12 months. At baseline, mean±SD of FACIT was 33.2±53.8 for women and 40.2±65.5 for men. After 12 months, mean±SD of FACIT was 34.5±55.8 for women and 44.5±72.4 for men.

The percentage of anorexic patients was 5.5% (FAACT score ≤24) and mean±SD of FAACT was 37.0±33.6 at baseline and after 12 months (p>0.05). At baseline, mean±SD of FAACT was 35.4±31.9 for women and 38.7±35.4 for men. After 12 months, mean±SD of FAACT was 34.8±31.5 for women and 39.3±35.8 for men.

Low fat-free mass index analysis (ALMI <5.45 kg/m^2 for women and <7.25 kg/m^2 for men) showed that seven women (9%) had lean tissue depletion and no man (0%) had lean tissue depletion at baseline. After 12 months, we found six women (8.3%) and no man (0%)

with lean tissue depletion. Disease duration and ALMI presented significant negative association (r=-0.3; p<0.05) at baseline. Additionally, disease activity status was associated with changes on ALMI (p<0.05; table 2). Women in remission showed higher ALMI than women in non-remission (p<0.05). The treatment with bDMARDs was not related with changes on ALMI (NS; table 3).

The evaluation of blood analyses demonstrated a CRP median of 3.9 mg/l (IQR 1.8-9.3), IL-6 median of 14.9 pg/ml (IQR 6.2-41.7), mean±SD hemoglobin of 12.8±1.2 g/dl and median albumin of 4.4 g/dl (IQR 4.2-4.5) at baseline. After 12 months, we found CRP median of 3. 8 mg/l (IQR 1.3-9.9), IL-6 median of 14.9 pg/ml (IQR 6.9-36.6), mean±SD hemoglobin of 12.7±1.1 g/dl and median albumin of 4.4 g/dl (IQR 4.1-4.4). After 12 months, only albumin levels were significantly decreased (p<0.05).

Factors associated to RC or classical cachexia

Eleven RA patients (12.2%) showed low $ALMI_{FMI}$ for age (Z-score ≤-1) at baseline, and 13 (16.0%) after 12 months. At baseline, we did not find association of $ALMI_{Z,}$ FMI_z and $ALMI_{FMI}$ with physical function (NS). After 12 months, $ALMI_{FMI}$ was negatively associated with HAQ-DI (r=-0.3; p<0.05). Disease activity status was associated with changes in $ALMI_{Z,}$ FMI_z and $ALMI_{FMI}$ (p<0.05; table 2). Women in remission showed higher $ALMI_Z$ than women in non-remission (p<0.05; table 2). Men in remission increased FMI_z after one-year follow-up (p<0.001; table 2) and showed higher FMI_z than men in non-remission after 12 months (p<0.05; table 2). Women in remission showed higher $ALMI_{FMI}$ than women in non-remission (p<0.001; table 2). Although not statistically significant, $ALMI_{FMI}$ of RA patients treated with bDMARDs was numerically higher than $ALMI_{FMI}$ of patients non-treated with bDMARDs at both times (table 3). The use of bDMARDs was not related with alterations in $ALMI_Z$, FMI_z and $ALMI_{FMI}$ (p>0.05; table 3).

In physical function parameters, we found positive association between HAQ-DI and DAS-28 at baseline and after 12 months (r=0.6, p<0.001 in both times). Also, we found positive association between HAQ-DI and FMI at baseline (r= 0.3; p<0.05) and after 12 months (r= 0.2; p<0.05). At 12 months, we found negative association between HAQ-DI and $ALMI_{FMI}$ (r=-0.3; p<0.05). Disease activity status was associated with changes on HAQ-DI-DI scores (p<0.05; table 4). Women in non-remission showed higher disability than men in non-remission (p<0.001; table 4). In addition, women in remission showed less disability than women in non-remission (p<0.001; table 4). It was not possible to test the effect of treatment with bDMARDs on HAQ-DI, due to the low sample sizes (table 4).

Low gait speed (<0.8m/s) was observed at baseline and after 12 months. Eighty-four patients (93.3%) had low gait speed at baseline, while 75 patients (93.8%) had low gait speed after 12 months. Additionally, gait speed was negatively associated with DAS-28 (r=-0.4; p<0.001) at baseline and after 12 months (r=-0.3; p<0.001). Women showed lower gait speed than men (p<0.001; table 4). The treatment with bDMARDs was associated with changes on

gait speed (p<0.05; table 4). Men treated with bDMARDs showed lower gait speed than men non-treated with bDMARDs (p<0.05; table 3).

Low muscle strength of the lower limbs (number of chair stands in 30 s <12 for women and <14 for men) was observed at baseline and after 12 months. Seventy-two women (92.3%) and twelve men (100.0%) showed low muscle strength of the lower limbs at baseline. After 12 months, sixty-six women (91.7%) and seven men (77.8%) showed low muscle strength of the lower limbs. Additionally, low muscle strength of the lower limbs was negatively associated with DAS-28 (r=-0.4; p<0.001) at baseline and after 12 months (r=-0.3; p<0.001). Disease activity status and treatment with bDMARDs were associated with changes in muscle strength of the lower limbs (p<0.05; table 4). Women in remission showed higher number of repetitions than women in non-remission (p<0.05; table 4). Women treated with bDMARDs showed lower number of repetitions than women non-treated with bDMARDs (p<0.001; table 4). Men treated with bDMARDs showed lower number of repetitions than men non-treated with bDMARDs (p<0.001; table 4).

Regarding blood glucose and lipid profile analysis, LDL levels declined after 12 months (p<0.05), although TC and TG levels remained unchanged (p<0.05). Laboratory data are described in table 5.

Table 2: Generalized estimating equations (GEE) analysis and body composition parameters in RA patients

		Baseline (n=90)		At 12 months (n=81)	
		Women (n=78) Mean (SE)	Men (n=12) Mean (SE)	Women (n=72) Mean (SE)	Men (n=9) Mean (SE)
Body Weight (kg)	Remission[1]	68.9 (1.5)	78.4 (4.4)	71.0 (1.8)	78.4 (4.4)
	Non-remission[2]	68.8(1.7)	74.7 (3.7)	69.7 (1.6)	74.3 (3.5)
BMI (kg/m^2)	Remission	27.7 (0.6)	26.4 (1.5)	28.8 (0.7)	26.9 (1.5)
	Non-remission	27.6 (0.6)	25.3 (1.1)	28.3 (0.6)	25.4 (1.0)
FMI (kg/m^2)	Remission	11.2 (0.4)$^{\#}$	7.2 (1.2)$^{\#}$	12.1 (0.5)	7.6 (1.3)
	Non-remission	11.5 (0.5)	6.1 (0.9)	11.8 (0.4)	5.9 (0.8)
FFMI (kg/m^2)	Remission	16.0 (0.2)*	18.7 (0.4)	16.4 (0.2)*	18.7 (0.5)
	Non-remission	15.9 (0.2)	19.3 (0.4)	15.9 (0.2)	19.3 (0.4)
ALMI (kg/m^2)	Remission	6.5 (0.1)	8.2 (0.2)	6.5 (0.1)	8.2 (0.1)
	Non-remission	6.4 (0.1)	8.4 (0.2)	6.3 (0.1)	8.2 (0.2)
ALM_Z	Remission	0.0 (0.1)*	- 0.3 (0.1)	0.0 (0.1)*	- 0.2 (0.1)
	Non-remission	- 0.1 (0.1)	-0.0 (0.2)	- 0.2 (0.1)	-0.2 (0.1)
FMI_Z	Remission	- 0.4 (0.1)	-1.0 (0.5)$^{\#}$	- 0.2 (0.1)	- 0.6 (0.5)*
	Non-remission	-0.2 (0.1)	- 1.0 (0.4)	- 0.3 (0.1)	- 1.3 (0.4)
$ALMI_{FMI}$ Z	Remission	0.5 (0.1)*	0.2 (0.5)	0.4 (0.1)*	0.1 (0.5)
	Non-remission	0.1 (0.1)	0.6 (0.4)	0.1 (0.1)	0.6 (0.3)

*difference between remission and non-remission (p<0.05); $^{\#}$difference between baseline and 12 months (p<0.05);† difference between gender (p<0.05).[1] Remission = 18 RA patients at baseline and 15 RA patients at 12 months [2]; Non- remission = 72 RA patients at baseline and 66 RA patients at 12 months.

Table 3: Generalized estimating equations (GEE) analysis and body composition parameters in RA patients

		Baseline (n=90)		At 12 months (n=81)	
		Women (n=78) Mean (SE)	Men (n=12) Mean (SE)	Women (n=72) Mean (SE)	Men (n=9) Mean (SE)
Body Weight (kg)	Treated with bDMARDs[3]	68.0 (2.0)	72.0 (13.4)	69.3 (2.0)	72.5 (13.1)
	Non-treated with bDMARDs[4]	69.2 (1.6)	77.2 (3.6)	70.3 (1.6)	75.3 (2.8)
	Treated with bDMARDs	27.2 (0.7)	24.1 (2.4)	28.0 (0.7)	24.7 (2.4)
	Non-treated with bDMARDs	27.8 (0.6)[#]	26.1 (1.3)	28.6 (0.6)	25.7 (1.0)
FMI (kg/m^2)	Treated with bDMARDs	11.3 (0.5)	4.7 (1.9)	11.8 (0.5)	4.6 (1.8)
	Non-treated with bDMARDs	11.6 (0.5)	7.0 (1.2)	11.9 (0.5)	6.5 (0.8)
FFMI (kg/m^2)	Treated with bDMARDs	15.7 (0.2)	19.3 (0.4)[#]	15.8 (0.2)	20.2 (0.6)
	Non-treated with bDMARDs	15.9 (0.2)	19.0 (0.4)	16.1 (0.2)	18.9 (0.4)
ALMI (kg/m^2)	Treated with bDMARDs	6.3 (0.1)	8.0 (0.2)	6.4 (0.1)	8.3 (0.2)
	Non-treated with bDMARDs	6.3 (0.1)	8.3 (0.2)	6.4 (0.1)	8.1 (0.2)
ALM_Z	Treated with bDMARDs	- 0.1 (0.1)	- 0.1 (0.2)	- 0.2 (0.1)	- 0.03 (0.1)
	Non-treated with bDMARDs	- 0.1 (0.1)	- 0.1 (0.1)	- 0.2 (0.1)	- 0.2 (0.1)
FMI_Z	Treated with bDMARDs	- 0.3 (0.1)	- 1.6 (0.9)	- 0.2 (0.1)	-1.9 (1.0)
	Non-treated with bDMARDs	- 0.3 (0.1)	- 0.9 (0.5)	- 0.3 (0.1)	- 0.9 (0.5)
$ALMI_{FMI}$ Z	Treated with bDMARDs	0.3 (0.1)	0.9 (0.3)	0.2 (0.2)	1.2 (0.4)
	Non-treated with bDMARDs	0.2 (0.1)	0.4 (0.5)	0.1 (0.1)	0.3 (0.4)

‡difference between treated with bDMARDs and non-treated with bDMARDs ($p<0.05$); [#]difference between baseline and 12 months ($p<0.05$);[†] difference between gender ($p<0.05$). [3]Patients treated with bDMARDs = 27 RA patients at baseline and 29 RA patients at 12 months; [4] Patients non-treated with bDMARDs = 63 RA patients at baseline and 52 RA patients at 12 months.

Table 4: Generalized estimating equations (GEE) analysis of physical function of RA patients

		Baseline (n=90)		12 months (n=81)	
		Women (n=78) Mean (SE)	Men (n=12) Mean (SE)	Women (n=78) Mean (SE)	Men (n=12) Mean (SE)
HAQ-DI scores	Remission[1]	0.5(0.1)*	1.1 (0.5)	0.5(0.1)*	0.7(0.2)
	Non-remission[2]	1.3(0.1)†	0.6(0.3)	1.2(0.1)†	0.7(0.2)
	Treated with bDMARDs[3]	-	-	-	-
	Non-treated with bDMARDs[4]	-	-	-	-
Gait Speed (m/s)	Remission	0.5 (0.0) †	0.7 (0.1)	0.6 (0.0) †	0.9 (0.1)
	Non-remission	0.5 (0.0) †	0.7 (0.0)	0.6 (0.0) †	0.7 (0.0)
	Treated with bDMARDs	0.5 (0.0) †	0.6 (0.0) ‡	0.6 (0.0) †	0.6 (0.0) ‡
	Non-treated with bDMARDs	0.5 (0.0) †	0.7 (0.0)	0.6 (0.0) †	0.8 (0.0)
30seg STS (repetitions)	Remission	10.4 (0.4)*	11.1 (0.6)	10.6 (0.5)*	10.9 (1.0)
	Non-remission	9.6 (0.4)	12.1 (0.5)	9.7 (0.3)	12.6 (0. 9)
	Treated with bDMARDs	10.3 (0.6) †	10.5 (0.3)	10.1 (0.5)†	10.0 (0.0)
	Non-treated with bDMARDs	9.5 (0.4)	11.9 (0.5)	9.8 (0.4)	12.8 (0.8)

*difference between remission and non-remission ($p<0.05$); ‡ difference between treated with bDMARDs and non-treated with bDMARDs ($p<0.05$)†; #difference between baseline and 12 months ($p<0.05$);† difference between gender ($p<0.05$). [1]Remission = 18 RA patients at baseline and 15 RA patients at 12 months; [2]Non- remission = 72 RA patients at baseline and 66 RA patients at 12 months; [3]Patients treated with bDMARDs = 27 RA patients at baseline and 29 RA patients at 12 months; [4]Patients non-treated with bDMARDs = 63 RA patients at baseline and 52 RA patients at 12 months.

Table 5 – Blood glucose and lipid profile analysis of RA patients

Parameters	Baseline (n=81)	12 Months (n=81)	P
Glucose (mg/dl)	87.5 (80.7 – 92.5)	91.0 (84.0 – 100.0)	0.000*
Total cholesterol (mg/dl)	202.0 (176.2 – 221.2)	193.0 (173.0 – 213.0)	NS
HDL (mg/dl)	51.0 (44.0 – 62.0)	52.0 (44.5 – 62.5)	NS
LDL (mg/dl)	120.2 (98.3 – 138.2)	108.8 (83.9 – 130.9)	0.003*
Triglycerides (mg/dl)	122.5 (80.0 – 165.2)	116.0 (90.0 – 163.0)	NS

p, The pairwise T Student Test;* Wilcoxon test $p<0.05$. HDL cholesterol, high-density cholesterol ; LDL cholesterol, low-density cholesterol.

DISCUSSION

The main findings of this study were that the RC prevalence was found in 13% of RA patients using Engvall criteria and 30% using Elkan criteria (14). The assessment of classical cachexia prevalence using Evans criteria (15) showed that none of our patients were cachectic. In addition, there was no significant difference in RC and classical cachexia prevalence between baseline and 12 months by both diagnostic criteria.

To the best of our knowledge, this is the first study that assessed prevalence of RC, prevalence of classical cachexia and factors associated over one-year follow-up in RA patients. We demonstrated that RC prevalence did not change after one-year follow-up, but significant changes in physical function and body composition were observed.

In a recent meta-analysis, Santo et al (16) demonstrated that there is a great variability in RC prevalence in the literature, and this variability depends on the different diagnostic criteria used for RC classification, as well as method of body composition assessment. The meta-analysis showed an estimated RC prevalence of 32% using the criteria defined by Engvall (13) and the body composition assessment by DXA (16). In this study, however, we found 13% of RC prevalence using Engvall criteria. It has been demonstrated that inflammation is associated with changes in body composition in RA patients (10,36). Thus, the difference in RC prevalence between the studies may be related to the disease activity status, since our patients presented moderate disease activity, while most patients from thestudies included in the meta-analysis had high disease activity (16).

In contrast, using the diagnostic criteria defined by Elkan (14), the RC prevalence was similar to Santo et al (16). Following these criteria (14), we demonstrated that RC was present in about 30% of the patients at baseline and in 24.4% of the patients after one-year follow-up. The meta-analysis of articles using the criteria defined by Elkan et al (14) and the body composition assessment by DXA included one study in which RA patients had moderate disease activity. Thus, the estimated prevalence of RC was lower (29%), demonstrating that disease status is important to RC condition.

The disease activity status also affects specific measures of body composition. Tournadre et al (37) compared body composition of high disease activity RA patients with control individuals and reported decreased FFMI and not modified fat composition. Yet, Lemmey et al (38) reported that low disease activity RA patients have lower total lean mass and higher total fat mass, in comparison with healthy controls. We found increased FFMI in women in remission and in men treated with bDMARDs after one-year follow-up, demonstrating that the improvement in FFMI is linked to disease activity and treatment. Accordingly, other studies demonstrated that the treatment with bDMARDs, such as tocilizumab and etanercept, favors the increase of FFMI proportion in RA patients (37,39). Despite these results, none of the studies assessed body composition taking gender into account.

According to the classical cachexia defined by Evans criteria (15) none of our patients were classified as cachectic. As far as we know, van Bokhorst et al (40) were the only group

that applied Evans criteria and they reported that 1% of RA patients were cachectic. In our study, only five patients showed low BMI (<20 kg/m^2) at baseline, however, they did not show other alterations that are necessary for the classical cachexia diagnosis. Literature shows that physical inactivity (41) and pharmacological treatment (37,42,43), due to the effective reversal of the systemic inflammatory process, seem to affect the gain or the maintenance of body weight in RA patients. In the present cohort, women showed increased body weight and BMI and approximately 50% of our patients were treated with glucocorticoid. Popescu et al (44) demonstrated higher prevalence of overweight in RA group in comparison with matched controls. They suggest that low-dose glucocorticoid treatment seems to contribute to adiposity gain and redistribution. Therefore, as weight loss is the main outcome for Evans' diagnostic criteria (15), and RA patients rarely present weight loss, the cachexia prevalence using this criteria is extremely low or nonexistent.

Muscle strength is a component of classical cachexia criteria and, in our study, it showed major changes, with significant reduction over time. Considering the European cut-off point for muscle strength, our patients showed low muscle strength (26) at baseline and after 12 months, independently of disease status or treatment used. Studies reported that RA patients show lower muscle strength than healthy controls (38) and that the low muscle strength is associated with disease activity (45). According to Yamada et al (46), intracellular (intrinsic) muscle dysfunction plays an important role in the underlying mechanism of muscle weakness associated with RA.

Although we found low muscle strength in our study, few patients presented low ALMI. Otherwise, our results indicate that remission have effect on ALMI. Women in remission showed higher ALMI than women in non-remission, demonstrating that the active inflammatory process favors muscle mass loss, corroborating with Roubenoff et al (17). Lemmey et al (42) did not find significant difference between RA patients in remission and non-remission. The inclusion of a greater number of male patients, in comparison with our study, may explain the results of Lemmey's study (42), once it is known that men have higher ALMI than women.

Other factors related to RC or classical cachexia were evaluated. It is known that adiposity is an important confounder that may mask true relationships between physical functioning and ALMI (29). Thus, Weber et al (29) proposed the new parameter where ALMI and FMI were used to generate sex, and race-specific standard deviation scores (Z-Scores): $ALMI_z$ for the FMI_z. Additionally, adiposity-adjusted ALMI Z-scores ($ALMI_{FMI}$) were generated by utilizing the residuals from the regression of ALMI Z-score on FMI Z-score. Baker et al showed that RA patients have low $ALMI_Z$, FMI_Z and $ALMI_{FMI}$. Analyzing the effects of DAS-28 and treatment with bDMARDs on body composition parameters, we found low $ALMI_Z$ and FMI_z. Roubenoff et al (17,47) described that patients with high disease activity RA have low body cell mass, which is possibly happening to our patients in non-remission. In addition, we found negative association between $ALMI_{FMI}$ and HAQ-DI after 12 months, corroborating with Baker et al study (29) and demonstrating the relationship of disability and low fat-adjusted lean mass for age.

Besides the body composition parameters assessed as factors related to RC or classical cachexia, we also assessed physical function by gait speed and muscle strength of the lower limbs. Low physical function over time was an important finding of our study. Independently of disease status, our RA patients had gait speed below 0.8m/s, which is considered low gait speed according to the literature (26). Additionally, in 30second-sit-stand test, our patients showed levels of muscle strength of the lower limbs similar to people aged between 80 and 84 years (48), at baseline and after 12 months. Accordingly, Lemmey et al (38) found decreased muscle strength of the lower limbs of RA patients in comparison with healthy controls. Also, they reported that non-remission RA patients had muscle strength of the lower limbs in comparison with both remission RA patients and healthy controls. Our results show that physical function of RA patients is also an important feature affected by the disease activity and, therefore, this condition deserves clinical attention. Lastly, the RA patients in non-remission showed larger disability than RA patients in remission, mainly the women. Lemmey et al (38) also compare RA patients in remission with patients in non-remission and they found larger disability in RA patients in non-remission. Thus, disease activity directly affects disability.

A limitation of the present study was the absence of a control group with healthy individuals matched by age and gender. A control group would be useful to better evaluate the impact of RA versus normal variations on physical function and body composition over time. Another point was disease activity score. Our patients had a mild, but statistically significant, increase in the disease activity score during the 12 months. Despite this increase in disease activity, the patients remained in moderate category. This fact may have influenced the few changes in RA patients' outcomes after 12 months.

In conclusion, in this cohort of established RA patients, RC was significantly present, but no classical cachexia was identified. RC and other factors related with RC or classical cachexia, mainly physical function, may be influenced by disease status and bDMARDs use. These finds stress the importance of adequate control of disease activity at early stages of the disease. Thus, cohort studies are important to assess the impact of RC in RA patients.

ACKNOWLEDGEMENT

We thank the Coordination for the Improvement of Higher Level Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES) and the Foundation for Research Support of the Rio Grande do Sul State (Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul - FAPERGS) for granting scholarships to the students that contributed to the development of this study. Also, we thank the Service of Rheumatology and Service of Biostatistics of HCPA by financial and scientific support. This study was supported by the Research and Events Incentive Fund of HCPA (Fundo de Incentivo à Pesquisa e Eventos-FIPE do HCPA), the Research Support Fund of Rheumatology Society of the Rio Grande do Sul (Fundo de Apoio à Pesquisa da Sociedade de Reumatologia do Rio Grande do Sul) and

National Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico-CNPq).

CONFLICT OF INTEREST

None declared

ETHICAL GUIDELINES

The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. Reference: von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. J Cachexia Sarcopenia Muscle 2015; 6: 315–316.

REFERENCES

1. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Prim. 2018;4:18001.
2. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;358:903–11.
3. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum. 2010;62(6):1576–82.
4. Tobón GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. J Autoimmun. 2010;35(1):10–4.
5. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: Estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014;73(7):1316–22.
6. Rodrigues AM. Tools for the Assessment of Comorbidity Burden in Rheumatoid Arthritis. 2018;5:1–7.
7. Norton S, Koduri G, Nikiphorou E, Dixey J, Williams P, Young A. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in ra and their impact on outcome. Rheumatology. 2013;52(1):99–110.
8. Roubenoff R, Rall LC. Humoral mediation of changing body composition during aging and chronic inflammation. Nutr Rev. 1993;51:1–11.
9. Rall LC, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. Rheumatology. 2004;43(10):1219–23.
10. Walsmith J, Abad L, Kehayias J, Roubenoff R. Tumor necrosis factor-alpha production is associated with less body cell mass in women with rheumatoid arthritis. J Rheumatol. 2004;31(1):23–9.
11. Roubenoff R. Rheumatoid cachexia: a complication of rheumatoid arthritis moves into the 21st century. Arthritis research & therapy. 2009. p. 108.
12. Walsmith J, Roubenoff R. Cachexia in rheumatoid arthritis. Int J Cardiol. 2002;85(1):89–99.
13. Engvall IL, Elkan AC, Tengstrand B, Cederholm T, Brismar K, Hafstrom I. Cachexia in rheumatoid arthritis is associated with inflammatory activity, physical disability, and low

bioavailable insulin-like growth factor. Scand J Rheumatol. 2008;37(5):321–8.

14. Elkan A-C, Hakansson N, Frostegard J, Cederholm T, Hafstrom I. Rheumatoid cachexia is associated with dyslipidemia and low levels of atheroprotective natural antibodies against phosphorylcholine but not with dietary fat in patients with rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther. 2009;11(2):R37.

15. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: A new definition. Clin Nutr. 2008;27(6):793–9.

16. Santo RCE, Fernandes KZ, Lora PS, Filippin LI, Xavier RM. Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2018;

17. Roubenoff R, Roubenoff R a, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest. 1994;93(6):2379–86.

18. El Maghraoui A, Sadni S, Rezqi A, Bezza A, Achemlal L, Mounach A. Does rheumatoid cachexia predispose patients with rheumatoid arthritis to osteoporosis and vertebral fractures? J Rheumatol. 2015;42(9):1556–62.

19. Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, Sandoo A, Toms TE, Nevill AM, et al. Rheumatoid cachexia and cardiovascular disease. Clin Exp Rheumatol. 2009;27(6):985–8.

20. Hugo M, Cetre NM, Pierreisnard A, Schaeverbeke T, Gin H, Rigalleau V. Energy expenditure and nutritional complications of metabolic syndrome and rheumatoid cachexia in rheumatoid arthritis: An observational study using calorimetry and actimetry. Rheumatol. 2016;55(7):1202–9.

21. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.

22. Strand V, Rentz AM, Cifaldi M a, Chen N, Roy S, Revicki D. Health-related quality of life outcomes of adalimumab for patients with early rheumatoid arthritis: results from a randomized multicenter study. J Rheumatol. 2012;39(1):63–72.

23. Baker JF, Von Feldt JM, Mostoufi-Moab S, Kim W, Taratuta E, Leonard MB. Insulin-like Growth Factor 1 and Adiponectin and Associations with Muscle Deficits, Disease Characteristics, and Treatments in Rheumatoid Arthritis. J Rheumatol. 2015;42(11):2038–45.

24. Schutz Y, Kyle UUG, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y. Int J Obes Relat Metab Disord. 2002;26:953–60.

25. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Vol. 854, World Health Organization technical report series. 1995. p. 1–452.

26. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis. Age Ageing. 2010;39(4):412–23.

27. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005;32(5):811–9.

28. Chang VT, Xia Q, Kasimis B. The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) Appetite Scale in veteran cancer patients. J Support Oncol. 3(5):377–82.

29. Weber D, Long J, Leonard MB, Zemel B, Baker JF. Development of Novel Methods to

Define Deficits in Appendicular Lean Mass Relative to Fat Mass. PLoS One. 2016;11(10):e0164385.

30. Baker JF, Giles JT, Weber D, Leonard MB, Zemel BS, Long J, et al. Assessment of muscle mass relative to fat mass and associations with physical functioning in rheumatoid arthritis. Rheumatology. 2017;56(6):981–8.

31. Kojima T, Ishikawa H, Tanaka S, Haga N, Nishida K, Yukioka M, et al. Validation and reliability of the Timed Up and Go test for measuring objective functional impairment in patients with long-standing rheumatoid arthritis: A cross-sectional study. Int J Rheum Dis. 2017;5.

32. Santana FS, Cunha Nascimento D, Freitas JPM, Miranda RF, Muniz LF, Neto LS, et al. Assessment of functional capacity in patients with rheumatoid arthritis: Implications for recommending exercise. Rev Bras Reumatol. 2014;54(5):378–85.

33. Unver B, Kahraman T, Kalkan S, Yuksel E, Karatosun V, Gunal I. Test-retest reliability of the stair test in patients with total hip arthroplasty. Hip Int. 2015;25(2):160–3.

34. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). 2005;

35. Masuko K. Rheumatoid cachexia revisited: a metabolic co-morbidity in rheumatoid arthritis. Front Nutr. 2014;1:20.

36. Binymin K, Herrick A, Carlson G, Hopkins S. The effect of disease activity on body composition and resting energy expenditure in patients with rheumatoid arthritis. J Inflamm Res. 2011;4:61–6.

37. Tournadre A, Pereira B, Dutheil F, Giraud C, Courteix D, Sapin V, et al. Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. J Cachexia Sarcopenia Muscle. 2017;8(4):639–46.

38. Lemmey AB, Wilkinson TJ, Clayton RJ, Sheikh F, Whale J, Jones HSJ, et al. Tight control of disease activity fails to improve body composition or physical function in rheumatoid arthritis patients. Rheumatology. 2016;55(10):1736–45.

39. Marcora SM, Chester KR, Mittal G, Lemmey AB, Maddison PJ. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr. 2006 Dec;84(6):1463–72.

40. van Bokhorst - de van der Schueren MAE, Konijn NPC, Bultink IEM, Lems WF, Earthman CP, van Tuyl LHD. Relevance of the new pre-cachexia and cachexia definitions for patients with rheumatoid arthritis. Clin Nutr. 2012;31(6):1008–10.

41. Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Panoulas VF, Douglas KMJ, Jamurtas AZ, et al. What predicts obesity in patients with rheumatoid arthritis An investigation of the interactions between lifestyle and inflammation. Int J Obes. 2010;34(2):295–301.

42. Baker JF, Sauer BC, Cannon GW, Teng C-C, Michaud K, Ibrahim S, et al. Changes in Body Mass Related to the Initiation of Disease-Modifying Therapies in Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(8):1818–27.

43. Jurgens MS, Jacobs JWG, Geenen R, Bossema ER, Bakker MF, Bijlsma JWJ, et al. Increase of body mass index in a tight controlled methotrexate-based strategy with prednisone in early rheumatoid arthritis: Side effect of the prednisone or better control of disease activity? Arthritis Care Res (Hoboken). 2013;65(1):88–93.

44. Popescu C, Bojincă V, Opriş D, Ionescu R. Dual X-ray absorptiometry whole body composition of adipose tissue in rheumatoid arthritis. Rom J Intern Med. 2015;53(3):1–11.

45. Palamar D, Er G, Terlemez R, Ustun I, Can G, Saridogan M. Disease activity, handgrip strengths, and hand dexterity in patients with rheumatoid arthritis. Clin Rheumatol.

2017;36(10):2201–8.

46. Yamada T, Steinz MM, Kenne E, Lanner JT. Muscle Weakness in Rheumatoid Arthritis: The Role of Ca2 +and Free Radical Signaling. EBioMedicine. 2017;23:12–9.

47. Roubenoff R, Roubenoff RA, Ward LM, Holland SM, Hellmann DB. Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. J Rheumatol. 1992;19(10):1505–10.

48. Rikli RE, Jones CJ. Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. Gerontologist. 2013;53(2):255–67.

8. CONSIDERAÇÕES FINAIS

A revisão sistemática com meta-análise mostrou uma prevalência de caquexia de 15 a 32%, de acordo com diferentes critérios de diagnóstico e método de composição corporal utilizado, afirmando que esta condição é uma comorbidade frequente da artrite reumatoide.

Na coorte prospectiva de pacientes com AR, a prevalência de caquexia reumatoide utilizando os critérios de diagnóstico de Engvall e colaboradores foi de 13,3% na avaliação inicial e se manteve após 12 meses. Quando avaliado caquexia reumatoide pelos critérios de Elkan e colaboradores foi encontrado 30,0% dos pacientes com artrite reumatoide caquéticos. Após 12 meses, foi encontrado uma prevalência de 24,4% dos pacientes com artrite reumatoide caquéticos, no entanto, essa diferença não foi estatisticamente significativa. Quando avaliado caquexia clássica, não foi observado caquexia clássica em nenhum dos tempos.

Ao longo dos 12 meses, foram observadas associações do status de atividade da doença e do uso de tratamento biológico nas alterações dos parâmetros incluídos nos critérios de caquexia reumatoide. As alterações no índice de massa livre de gordura foi associado ao status de atividade da doença e ao uso de tratamento biológico, enquanto que, as alterações no Índice de massa de gordura foi associado apenas ao status de atividade da doença. Quanto analisado os parâmetros de caquexia clássica, foi observado associação do status de atividade da doença sobre a força muscular e índice de massa livre de gordura. Não foi observado anorexia e nem fadiga em ambos os tempos, no entanto, os marcadores inflamatórios estavam aumentados na avaliação inicial e após 12 meses.

Quando analisados as alterações de outros fatores relacionados à caquexia reumatoide e caquexia clássica ao longo de 12 meses, foi observado que o status de atividade da doença associou-se com massa magra ajustada pela gordura, capacidade funcional e força muscular de membros inferiores. Já o uso do tratamento biológico associou-se a velocidade de caminhada e a força muscular de membros inferiores. Quando analisados outros fatores laboratoriais, os níveis séricos de glicose aumentaram e os níveis séricos de

LDL reduziram após 12 meses, no entanto, esta modificação não foi clinicamente relevante.

As observações de que o estado de remissão está associado às alterações da função física e da composição corporal ao longo do tempo enfatizam a importância do controle adequado da atividade da doença. As observações sobre o efeito do tratamento biológico na caquexia foram controversas, demonstrando a necessidade de mais estudos avaliando estes parâmetros.

9. PERSPECTIVAS FUTURAS

A presente tese de doutorado gerou as seguintes perspectivas futuras, que já estão sendo desenvolvidas pelo grupo de pesquisa o Laboratório de Doenças Autoimunes em conjunto com o Serviço de Reumatologia do HCPA:

a) Avaliar o mesmo grupo de pacientes após cinco anos da primeira avaliação.
b) Analisar os níveis de miostatina e irisina no soro e no músculo de pacientes com artrite reumatoide;
c) Analisar as alterações moleculares, morfológicas e funcionais no músculo esquelético de pacientes com artrite reumatoide e de pacientes com osteoartrite;
d) Avaliar o perfil metabólico da urina de pacientes com AR e correlacionar com parâmetros de composição corporal em busca de possíveis biomarcadores para as alterações de composição corporal observadas na AR.

10. ANEXOS

10.1. ANEXO 1: TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado a participar do estudo “Aplicação e comparação dos critérios estabelecidos para diagnóstico para caquexia reumatoide” realizado pelo Serviço de Reumatologia do Hospital de Clínicas de Porto Alegre (HCPA).

A caquexia é uma doença que tem como sintoma a perda de peso corporal que pode se associar à artrite reumatoide e interferir na qualidade de vida dos pacientes. Como consequência, ela pode trazer limitações para as atividades do dia a dia. Este estudo tem como objetivo verificar qual o melhor critério para diagnosticar quais pacientes com artrite reumatoide possuem caquexia, através da avaliação de componentes como ossos, musculatura e gordura corporal, além de capacidade física, força muscular, cansaço durante o exercício, substâncias no sangue e na urina que podem indicar a caquexia em pacientes com artrite reumatoide. Você está sendo convidado a participar deste estudo porque possui o diagnóstico de artrite reumatoide e realiza tratamento no ambulatório do HCPA. Caso você aceite participar, será aplicada uma ficha para verificar algumas informações pessoais e clínicas. Também será aplicado um questionário de apetite (vontade de comer) e serão utilizadas informações do questionário de capacidade funcional (sobre a realização de atividades do dia a dia) que você já responde habitualmente nas suas consultas. Você poderá sentir algum desconforto ao responder perguntas pessoais ou relacionadas à sua vida, mas você poderá não responder qualquer pergunta que não se sinta à vontade. Você deve demorar em torno de 10 minutos para responder aos questionários da pesquisa.

Também será realizado um teste de levantar e sentar da cadeira, no qual você terá que sentar e levantar de uma cadeira 5 (cinco) vezes. Depois será

realizado um teste um teste de força de mão, no qual você terá que apertar um aparelho com a mão o mais forte que conseguir, e um teste de força de coxa, no qual você terá que empurrar um equipamento com a perna enquanto sentado. Durante estes testes você poderá se sentir cansado ou alguma dor ou desconforto, mas você poderá interromper a qualquer momento que desejar e estará sempre acompanhado pelo pesquisador capacitado. Você poderá sentir dor muscular pelo esforço do teste no dia seguinte, que deverá ser moderada e desaparecer em breve. Estes dois testes físicos devem durar em torno de 30 minutos.

Será combinado com você um dia para a realização dos exames que serão feitos no Centro de Pesquisa Clínica do HCPA. Para avaliação da estrutura corporal será realizado a densitometria corporal total, que é um exame parecido com uma radiografia (Rx), mas com radiação menor, com duração de seis minutos, indolor, sem utilização de contraste ou medicamento. O risco do exame de densitometria é a exposição à radiação, que é 10 vezes menor do que um raio X de tórax. E por fim, será realizada uma coleta de sangue e de urina no mesmo dia. A coleta de sangue será realizada através de punção venosa (picada na veia), que poderá causar alguma dor, desconforto ou hematoma (mancha roxa) que deverá desaparecer em alguns dias.

Após 6 meses, todos os questionários serão repetidos, em algum dia a combinar em que você vier realizar uma consulta habitual, e após 12 meses (1 ano) serão realizados novamente todos os questionários, testes e exames explicados acima. Não existem benefícios diretos pela sua participação neste estudo, mas você terá uma avaliação física mais específica do que já realizada assistencialmente. No entanto, participando deste estudo você ajudará na melhor compreensão da caquexia em pacientes com artrite reumatoide e esclarecendo ainda quais os melhores critérios para diagnosticar esta síndrome em pacientes com artrite reumatoide. Não estão previstos riscos adicionais além dos explicados acima, em cada procedimento da pesquisa que será realizado.

A participação no estudo é totalmente voluntária, a não participação ou desistência após ingressar no estudo não implicará em nenhum tipo de prejuízo

para o participante. Não está previsto nenhum tipo de pagamento pela participação no estudo e o participante não terá nenhum custo com respeito aos procedimentos envolvidos.

Os pesquisadores se comprometem em manter a confidencialidade dos dados de identificação pessoal dos participantes e os resultados serão divulgados de maneira agrupada, sem a identificação dos indivíduos que participaram do estudo.

Todas as dúvidas poderão ser esclarecidas antes e durante o curso da pesquisa, através de contato com o pesquisador responsável, Prof. Dr. Ricardo Machado Xavier no Serviço de Reumatologia do HCPA, no telefone (51) 3359 8340. O CEP/HCPA também poderá ser contatado para esclarecimento de dúvidas, no 2º andar do HCPA, sala 2227, ou através do telefone 33597640, das 8h às 17h, de segunda à sexta.

O documento será elaborado em duas vias, sendo uma delas entregue ao participante e outra mantida pelo grupo de pesquisadores.

COMPREENSÃO E AUTORIZAÇÃO

Depois de ler este termo e esclarecer minhas dúvidas, aceito participar deste estudo.

Participante:

_____

Assinatura: _____

Pesquisador:

_____

Assinatura do pesquisador:

_____

Porto Alegre, ____ de _____ de 20____.

10.2. ANEXO 2: ANAMNESE

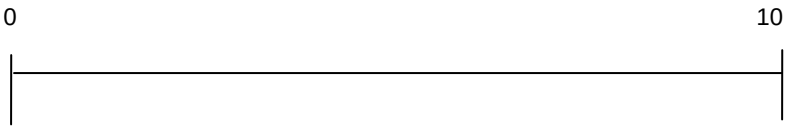
Data da avaliação	
Nome completo	
Prontuário	
Data de nascimento	
Idade	
Peso	
Estatura	

TESTES FÍSICOS

	1ª TENTATIVA	2ª TENTATIVA	3ª TENTATIVA
Preensão palmar - DIREITA			
Preensão palmar – ESQUERDA			
TUG			
Senta-levanta – 30s			

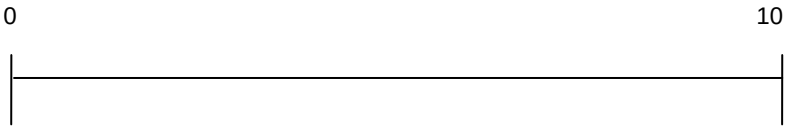
FAACT/FACIT-F			
QUESTÕES	VALOR	QUESTÕES	VALOR
28		48	
29		49	
30		50	
31		51	
32		52	
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			
47			

VAS DOR



Ausência de dor Dor insuportável

VAS FADIGA



Ausência de cansaço Cansaço insuportável

10.3. ANEXO 3: FUNCTIONAL ASSESSMENT OF ANOREXIA/CACHEXIA THERAPY (FAACT)

Abaixo encontrará uma lista de afirmações que outras pessoas com a sua doença disseram ser importantes. **Faça um círculo ou marque um número por linha para indicar a sua resposta no que se refere aos <u>últimos 7 dias</u>.**

<u>APETITE</u>	**Nem um pouco**	**Um pouco**	**Mais ou menos**	**Muito**	**Muitís-simo**
28-Tenho bom apetite	0	1	2	3	4
29-A quantidade que como é suficiente para satisfazer às minhas necessidades	0	1	2	3	4
30-Estou preocupado/a com o meu peso	0	1	2	3	4
31-A maior parte das comidas têm um sabor desagradável para mim	0	1	2	3	4
32-Ando preocupado/a por parecer tão magro/a	0	1	2	3	4
33-O meu interesse pela comida diminui mal começo a comer	0	1	2	3	4
34-Tenho dificuldade em comer alimentos ricos/gordurosos ou ‘pesados’	0	1	2	3	4
35-A minha família e os meus amigos teimam que eu coma	0	1	2	3	4
36-Tenho vomitado	0	1	2	3	4
37-Quando como parece que fico cheio/satisfeito/a rapidamente	0	1	2	3	4
38-Sinto dores na área do estômago	0	1	2	3	4
39-A minha saúde geral tem melhorado	0	1	2	3	4

10.4. ANEXO 4: THE FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT-F)

Abaixo encontrará uma lista de afirmações que outras pessoas com a sua doença disseram ser importantes. **Faça um círculo ou marque um número por linha para indicar a sua resposta no que se refere aos <u>últimos 7 dias</u>.**

FADIGA	**Nem um pouco**	**Um pouco**	**Mais ou menos**	**Muito**	**Muitíssi-mo**
40- Sinto-me fatigado/a	0	1	2	3	4
41- Sinto fraqueza generalizada	0	1	2	3	4
42- Sinto-me sem forças (sem vontade para nada)	0	1	2	3	4
43- Sinto-me cansado/a	0	1	2	3	4
44- Tenho dificuldade em <u>começar</u> as coisas porque estou cansado/a	0	1	2	3	4
45- Tenho dificuldade em <u>acabar</u> as coisas porque estou cansado/a	0	1	2	3	4
46- Tenho energia	0	1	2	3	4
47- Sou capaz de fazer as minhas a(c)tividades habituais	0	1	2	3	4
48- Preciso (de) dormir durante o dia	0	1	2	3	4
49- Estou cansado/a demais para comer	0	1	2	3	4
50- Preciso de ajuda para fazer as	0	1	2	3	4

minhas a(c)tividades habituais					
51- Estou frustrado/a por estar cansado/a demais para fazer as coisas que quero	0	1	2	3	4
52- Tenho que limitar as minhas a(c)tividades sociais por estar cansado/a	0	1	2	3	4

10.5. ANEXO 5: FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) LICENSING AGREEMENT

The Functional Assessment of Chronic Illness Therapy system of Quality of Life questionnaires and all related subscales, translations, and adaptations ("FACIT System") are owned and copyrighted by David Cella, Ph.D. The ownership and copyright of the FACIT System - resides strictly with Dr. Cella. Dr. Cella has granted FACIT.org (Licensor) the right to license usage of the FACIT System to other parties. Licensor represents and warrants that it has the right to grant the License contemplated by this agreement. The terms of this license will grant permission Licensor provides to ***Rafaela Espírito Santo*** **("Investigator")** *the licensing agreement outlined below.*

This letter serves notice that **RAFAELA ESPÍRITO SANTO** is granted license to use the **Portuguese** version of the **FAACT** in one study entitled:

This current license is only extended to RAFAELA ESPÍRITO SANTO's research project subject to the following terms:

(RAFAELA ESPÍRITO SANTO) agrees to provide Licensor with copies of any publications which come about as the result of collecting data with any FACIT questionnaire.

Due to the ongoing nature of cross-cultural linguistic research, Licensor reserves the right to make adaptations or revisions to wording in the FACIT, and/or related translations as necessary. If such changes occur, RAFAELA ESPÍRITO SANTO will have the option of using either previous or updated versions according to its own research objectives.

(RAFAELA ESPÍRITO SANTO) and associated vendors may not change the wording or phrasing of any FACIT document without previous permission from Licensor. If any changes are made to the wording or phrasing of any FACIT item without permission, the document cannot be considered the FACIT, and subsequent analyses and/or comparisons to other FACIT data will not be considered appropriate. Permission to use the name "FACIT" will not be granted for any unauthorized translations of the FACIT items. Any analyses or

publications of unauthorized changes or translated versions may not use the FACIT name. Any unauthorized translation will be considered a violation of copyright protection.

In all publications and on every page of the FACIT used in data collection, Licensor requires the copyright information be listed precisely as it is listed on the questionnaire itself.

This license is for paper administration only and is not extended to electronic data capture. Electronic versions of the FACIT questionnaires are considered derivative works and are not covered under this license. Permission for use of an electronic version of the FACIT must be covered under separate agreement between the electronic data capture vendor and FACIT.org

In no cases may any FACIT questionnaire be placed on the internet without password protection. To do so is considered a violation of copyright.

Licensor reserves the right to withdraw this license if RAFAELA ESPÍRITO SANTO engages in scientific or copyright misuse of the FACIT system of questionnaires.

There are no fees associated with this license.

This license is effective upon date issued by FACIT.org and expires at the completion of RAFAELA ESPÍRITO SANTO's project.

RAFAELA ESPÍRITO SANTO agrees to provide FACIT.org with a copy of any publication which results from this study.

Issued on: April 30, 2015Shannon C Romo

Assistant Business Manager

FACIT.org

381 S. Cottage Hill Avenue

Elmhurst, IL 60126 USA

10.6. ANEXO 6: FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) LICENSING AGREEMENT from FACIT.org

July 23, 2012

The Functional Assessment of Chronic Illness Therapy system of Quality of Life questionnaires and all related subscales, translations, and adaptations ("FACIT System") are owned and copyrighted by David Cella, Ph.D. The ownership and copyright of the FACIT System - resides strictly with Dr. Cella. Dr. Cella has granted FACIT.org (Licensor) the right to license usage of the FACIT System to other parties. Licensor represents and warrants that it has the right to grant the License contemplated by this agreement. Licensor provides to Rafaela Cavalheiro do Espírito Santo at the Hospital de Clinicas de Porto Alegre (COMPANY) the licensing agreement outlined below. If agreed to, this license will grant permission to Rafaela Cavalheiro do Espírito Santo at the Hospital de Clinicas de Porto Alegre the right to use the FACIT subscale to the extent outlined below.

This proposal outlines the licensing terms for Rafaela Cavalheiro do Espírito Santo at the Hospital de Clinicas de Porto Alegre to use the FACIT -F questionnaires(s) in the following languages in one (1) clinical trial (insert trial number here, if known) for the duration of the entire trial. The languages and costs are below:

FACIT-F

Portuguese - $0

Total = $0 USD

Licensing fee has been waived for this study only.

This current license extends to (COMPANY) subject to the following terms:

1) (COMPANY) agrees to complete a FACIT collaborator's form on our website, www.FACIT.org. (COMPANY) is not required to provide any

proprietary or confidential information on the website. Licensor agrees to use the information in the website database for internal tracking purposes only.

2) (COMPANY) agrees to provide Licensor with copies of any publications which come about as the result of collecting data with any FACIT questionnaire.

3) Due to the ongoing nature of cross-cultural linguistic research, Licensor reserves the right to make adaptations or revisions to wording in the FACIT, and/or related translations as necessary. If such changes occur, (COMPANY) will have the option of using either previous or updated versions according to its own research objectives.

4) (COMPANY) and associated vendors may not change the wording or phrasing of any FACIT document without previous permission from Licensor. If any changes are made to the wording or phrasing of any FACIT item without permission, the document cannot be considered the FACIT, and subsequent analyses and/or comparisons to other FACIT data will not be considered appropriate. Permission to use the name “FACIT” will not be granted for any unauthorized translations of the FACIT items. Any analyses or publications of unauthorized changes or translated versions may not use the FACIT name. Any unauthorized translation will be considered a violation of copyright protection.

5) In all publications and on every page of the FACIT used in data collection, Licensor requires the copyright information be listed precisely as it is listed on the questionnaire itself.

6) This license is not extended to electronic data capture vendors of (COMPANY). Electronic versions of the FACIT questionnaires are considered derivative works and are not covered under this license. Permission for use of an electronic version of the FACIT must be covered under separate agreement between the electronic data capture vendor and FACIT.org

7) This license is only extended for use on the internet on servers internal to (COMPANY). This FACIT license may not be used with online data capture

unless specifically agreed to by Licensor in writing. Such agreement will only be provided in cases where access is password protected.

8) Licensor reserves the right to withdraw this license if (COMPANY) engages in scientific or copyright misuse of the FACIT system of questionnaires.

9) In exchange for this license, (COMPANY) agrees to pay the fees outlined above.

Licensor agrees to defend, indemnify and hold COMPANY harmless from and against any and all liability, loss, damages, costs and expenses including but not limited to reasonable attorney fees arising from any claim or suit with regard to the infringement of any patient, copyright, trademark or other proprietary right infringement brought against COMPANY by reason of COMPANYs use of the FACIT questionnaire

Neither party shall use the name of the other party in any publicity, advertising or announcement without the consenting party’s prior written approval.

Licensor warrantees and represents that the terms of this Agreement are not inconsistent with any other contractual and/or legal obligations it may have or with its policies of the policies of any institution with which it is associated.

COMPANY: FACIT.org By: Jason Bredle

Title: Manager, Business Operations

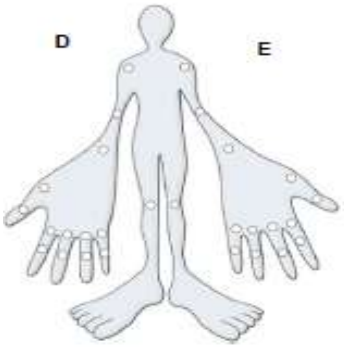
10.7. ANEXO 7: AVALIAÇÃO DA ATIVIDADE DA DOENÇA (Disease Activity Score- 28; DAS-28)

Centro de Referência em Artrite Reumatóide - HCPA

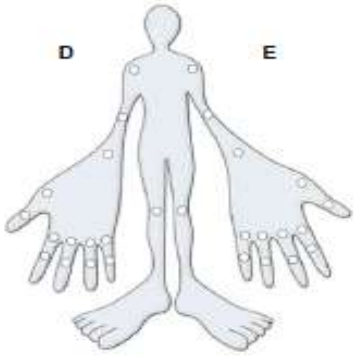
AVALIAÇÃO ARTICULAR

FOLHA DE AVALIAÇÃO ARTICULAR

Dolorosas



Inchadas



Dolorosas (0-28)	
Inchadas (0-28)	
Eritrossedimentação	
VAS atividade da doença segundo o paciente (0-100mm)	
DAS28	

ESCALA VISUAL ANALÓGICA

AVALIAÇÃO DO PACIENTE

DOR

Em média, quanta dor sentiu durante a última semana devido a sua doença?

0 — Sem Dor

100mm — A pior dor possível

Avaliação global do paciente em relação à atividade da doença

VAS

Considerando todas as formas como a artrite o afeta, em média, como tem se sentido durante a última semana?

0 — Muito bem

100 mm — Muito mal

AVALIAÇÃO DO MÉDICO

Avaliação global do médico em relação a atividade da doença
Como avalia a atividade da Artrite de seu paciente?

0 — Sem atividade

100 mm. — Atividade Intensa

10.8. ANEXO 8: QUESTIONÁRIO DE CAPACIDADE FUNCIONAL (Health Assessment Questionnaire; HAQ)

Centro de Referência em Artrite Reumatóide - HCPA

QUADRO 1
VERSÃO BRASILEIRA DO QUESTIONÁRIO DE CAPACIDADE FUNCIONAL HAQ-20

	Sem dificuldade	Com alguma dificuldade	Com muita dificuldade	Incapaz de fazer
01 Vestir-se, inclusive amarrar os cordões dos seus sapatos, abotoar as suas roupas?	0	1	2	3
02 Lavar a sua cabeça e os seus cabelos?	0	1	2	3
03 Levantar-se de uma maneira ereta de uma cadeira de encosto reto e sem braços?	0	1	2	3
04 Deitar-se e levantar-se da cama?	0	1	2	3
05 Cortar um pedaço de carne?	0	1	2	3
06 Levar à boca um copo ou uma xícara cheia de café, leite ou água?	0	1	2	3
07 Abrir um saco de leite comum?	0	1	2	3
08 Caminhar em lugares planos?	0	1	2	3
09 Subir cinco degraus?	0	1	2	3
10 Lavar seu corpo inteiro e secá-lo após o banho?	0	1	2	3
11 Tomar um banho de chuveiro?	0	1	2	3
12 Sentar-se e levantar-se de um vaso sanitário?	0	1	2	3
13 Levantar os braços e pegar um objeto de mais ou menos 2,5 quilos, que está posicionado um pouco acima de sua cabeça?	0	1	2	3
14 Curvar-se para pegar suas roupas no chão?	0	1	2	3
15 Segurar-se em pé no ônibus ou no metrô?	0	1	2	3
16 Abrir potes ou vidros de conserva que tenham sido previamente abertos?	0	1	2	3
17 Abrir e fechar torneiras?	0	1	2	3
18 Fazer compras na redondeza onde mora?	0	1	2	3
19 Entrar e sair de um ônibus?	0	1	2	3
20 Realizar tarefas tais como usar a vassoura para varrer e o rodo para puxar água?	0	1	2	3

QUADRO 2
AVALIAÇÃO DOS ESCORES DO HAQ-20

Componente 1 → (vestir-se)	Perguntas 1 e 2	→ Maior escore =
Componente 2 → (levantar-se)	Perguntas 3 e 4	→ Maior escore =
Componente 3 → (alimentar-se)	Perguntas 5, 6 e 7	→ Maior escore =
Componente 4 → (caminhar)	Perguntas 8 e 9	→ Maior escore =
Componente 5 → (higiene pessoal)	Perguntas 10, 11 e 12	→ Maior escore =
Componente 6 → (alcançar objetos)	Perguntas 13 e 14	→ Maior escore =
Componente 7 → (apreender objetos)	Perguntas 15, 16 e 17	→ Maior escore =
Componente 8 → (outras atividades)	Perguntas 18, 19 e 20	→ Maior escore =
		Média aritmética dos escores dos componentes =

10.9. PRODUÇÕES CIENTÍFICAS DURANTE O DOUTORAMENTO

Artigos

- SANTO, RAFAELA C.E.; FERNANDES, KEVIN Z. ; LORA, PRISCILA S. ; FILIPPIN, LIDIANE I. ; XAVIER, RICARDO M.. Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis. Journal of Cachexia Sarcopenia and Muscle, 2018.
- ALABARSE, PAULO V.G. ; LORA, PRISCILA S. ; SILVA, JORDANA M.S. ; SANTO, RAFAELA C.E. ; FREITAS, EDUARDA C. ; DE OLIVEIRA, MAYARA S. ; ALMEIDA, ANDRELISE S. ; IMMIG, MÔNICA ; TEIXEIRA, VIVIAN O.N. ; FILIPPIN, LIDIANE I. ; XAVIER, RICARDO M. . Collagen-induced arthritis as an animal model of rheumatoid cachexia. Journal of Cachexia Sarcopenia and Muscle, v. 9, p. 603-612, 2018.
- SANTO, R. C. E.; GAVA, M. P. ; BINI, R. R. ; OLSZEWSKI, V. ; TEIXEIRA, E. G. ; CHAKR, R. ; XAVIER, R. M. ; BRENOL, C. V. . NEUROMUSCULAR FATIGUE IS WEAKLY ASSOCIATED WITH PERCEPTION OF FATIGUE AND FUNCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS. RHEUMATOLOGY INTERNATIONAL, v. 38, p. 415-423, 2017.
- SANTO, R. C. E.; SILVA, J. M. S. ; TEIXEIRA, V. O. N. ; ALABARSE, P. V. G. ; FREITAS, E. C. ; FILIPPIN, L. I. ; LORA, P. S. ; XAVIER, R. M. . INDIVIDUALIZED MODERATE AEROBIC EXERCISE IMPROVES PHYSICAL CAPACITY AND PREVENTS WEIGHT LOSS IN COLLAGEN-INDUCED ARTHRITIS. International Journal of Clinical and Experimental Medicine, v. 9, p. 22696-22703, 2016.

Resumos publicados em anais de congressos

- SANTO, R. C. E.; SILVA, J. M. S. ; FILIPPIN, L. I. ; LORA, P. S. ; XAVIER, R. M. . DISEASE ACTIVITY AND FUNCTIONAL CAPACITY INFLUENCE FRAILTY IN RHEUMATOID ARTHRITIS PATIENTS. In: International Conference Frailty and Sarcopenia Research, 2018, Miami. The Journal of Frailty and Aging (JFA), 2018.
- SANTO, R. C. E.; SILVA, J. M. S. ; FILIPPIN, L. I. ; LORA, P. S. ; XAVIER, R. M. . FRAILTY IS ASSOCIATED WITH A MORE SEVERE DISEASE IN RHEUMATOID ARTHRITIS. In: Pan-American Congress of Rheumatology, 2018, Buenos Aires. Pan-American Congress of Rheumatology, 2018.
- SANTO, R. C. E.; SILVA, J. M. S. ; LORA, P. S. ; FILIPPIN, L. I. ; XAVIER, R. M. . DISEASE ACTIVITY AFFECTS FAT MASS INDEX AND FUNCTIONAL CAPACITY OF RA PATIENTS OVER 12 MONTHS. In: Annual European Congress of Rheumatology, 2018, Amsterdã. Annals of the Rheumatic Diseases (The EULAR Journal). UK: BMJ Publishing Group Ltd, 2018. v. 77. p. A1809-A1809.
- FERNANDES, K. Z. ; SANTO, R. C. E. ; FILIPPIN, L. I. ; XAVIER, R. M. . AVALIAÇÃO DA CAPACIDADE FUNCIONAL EM PACIENTES COM ARTRITE REUMATOIDE EM USO DE DROGAS BIOLÓGICAS OU SINTÉTICAS AO LONGO DE DOZE MESES.. In: 9° Congresso Internacional de Fisioterapia, 2017, Porto Alegre. Revista Brasileira de Crescimento e Desenvolvimento Humano, 2017.
- FERNANDES, K. Z. ; SANTO, R. C. E. ; FILIPPIN, L. I. ; LORA, P. S. ; XAVIER, R. M. . ASSOCIAÇÃO ENTRE ATIVIDADE DA DOENÇA, COMPOSIÇÃO CORPORAL E PARÂMETROS FUNCIONAIS EM PACIENTES COM ARTRITE REUMATOIDE. In: Semana Científica do Unilasalle (SEFIC), 2016, Canoas. XII SEMANA CIENTÍFICA UNILASALLE ? SEFIC 2016, 2016.
- CASTRO, J. R. S. ; SANTO, R. C. E. ; FERNANDES, K. Z. ; MACHADO, S. H. . MOTIVAÇÃO PARA PRÁTICA DESPORTIVA NA EDUCAÇÃO FÍSICA ESCOLAR EM

ADOLESCENTES COM ARTRITE IDIOPÁTICA JUVENIL OU LÚPUS ERITEMATOSO SISTÊMICO JUVENIL- RESULTADOS PRELIMINARES. In: 14º Congresso Brasileiro de Adolescência, 2016, Campo Grande. 14º Congresso Brasileiro de Adolescência, 2016.

- SANTO, R. C. E.; FERNANDES, K. Z. ; LORA, P. S. ; XAVIER, R. M. . AVALIAÇÃO DA FORÇA MUSCULAR, MASSA MUSCULAR, VELOCIDADE DA MARCHA E PARÂMETROS INFLAMATÓRIOS EM UMA COORTE DE PACIENTES COM ARTRITE REUMATOIDE. In: VI Congresso Brasileiro de Metabolismo, Nutrição e Exercício (CONBRAMENE), 2016, Londrina. VI Congresso Brasileiro de Metabolismo, Nutrição e Exercício (CONBRAMENE), 2016.
- SANTO, R. C. E.; MORO, A. L. ; FIGHERA, T. ; LORA, P. S. ; SPRITZER, P. M. ; XAVIER, R. M. . AVALIAÇÃO DA COMPOSIÇÃO CORPORAL EM PACIENTES COM ARTRITE REUMATOIDE EM USO DE DROGAS BIOLÓGICAS E SINTÉTICAS. In: Congresso Brasileiro de Densitometria Óssea, Osteoporose e Osteometabolismo, 2016, Joinville. Congresso Brasileiro de Densitometria Óssea, Osteoporose e Osteometabolismo, 2016.
- SANTO, R. C. E.; GAVA, M. P. ; BINI, R. R. ; OLSZEWSKI, V. ; TEIXEIRA, E. G. ; CHAKR, R. M. S. ; XAVIER, R. M. ; BRENOL, C. V. . CORRELATION BETWEEN PERCEPTION OF FATIGUE AND PERIPHERAL FATIGUE IN PATIENTS WITH RHEUMATOID ARTHRITIS. In: European League Against Rheumatism (EULAR), 2015, Roma. Annals of Rheumatic Diseases ARD, 2015.
- FREITAS, E. C. ; ALABARSE, P. V. G. ; LORA, P. S. ; SILVA, J. M. S. ; SANTO, R. C. E. ; ALMEIDA, A. S. ; TEIXEIRA, V. O. N. ; FILIPPIN, L. I. ; XAVIER, R. M. . COLLAGEN-INDUCED ARTHRITIS IN MICE AS A MODEL OF RHEUMATOID CACHEXIA. In: European League Against Rheumatism (EULAR), 2015, Roma. Annals of Rheumatic Diseases ARD, 2015.
- ALABARSE, P. V. G. ; TEIXEIRA, V. O. N. ; SILVA, J. M. S. ; SANTO, R. C. E. ; FREITAS, E. C. ; LORA, P. S. ; FILIPPIN, L. I. ; XAVIER, R. M. . AEROBIC EXERCISE IN INCLINED TREADMILL REDUCE FATIGUE IN COLLAGEN-INDUCED ARTHRITIS. In: European League Against Rheumatism (EULAR), 2015, Roma. Annals of Rheumatic Diseases ARD, 2015.
- SANTO, R. C. E.; ALABARSE, P. V. G. ; TEIXEIRA, V. O. N. ; SILVA, J. M. S. ; FREITAS, E. C. ; FILIPPIN, L. I. ; LORA, P. S. ; XAVIER, R. M. . INDIVIDUALIZED MODERATE AEROBIC EXERCISE IMPROVES PHYSICAL ENDURANCE AND PREVENTS WEIGHT LOSS IN COLLAGEN-INDUCED ARTHRITIS. In: 8 th International Conference on Cachexia, Sarcopenia & Muscle Wasting, 2015, Paris. Journal of Cachexia, Sarcopenia and Muscle, 2015. v. 6.

10.10. ANEXO 10: PRISMA 2009 CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	01
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	01
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	01 e 02
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	02
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	02
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	02
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	02
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	02
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	02
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	02

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	02
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	02
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	02
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	02 e 03
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	02
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	03
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	02
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	03-05
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	05 e 06
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	03-06
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	05
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	07
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	08
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	08
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	08 e 09

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

10.11. ANEXO 11: STROBE CHECKLIST

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	61
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	61
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	62
Objectives	3	State specific objectives, including any prespecified hypotheses	63
Methods			
Study design	4	Present key elements of study design early in the paper	63
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	63
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	63
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	63
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	63-65

Bias	9	Describe any efforts to address potential sources of bias	63
Study size	10	Explain how the study size was arrived at	66
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	66
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	66
		(*b*) Describe any methods used to examine subgroups and interactions	66
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	67
		(b) Give reasons for non-participation at each stage	67
		(c) Consider use of a flow diagram	67
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	67
		(b) Indicate number of participants with missing data for each variable of interest	67
		(c) Summarise follow-up time (eg, average and total amount)	67
Outcome data	15*	Report numbers of outcome events or summary measures over time	68-74

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	68-71
		(*b*) Report category boundaries when continuous variables were categorized	68-74
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	75
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	77
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	75-77
Generalisability	21	Discuss the generalisability (external validity) of the study results	77
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	77

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.