REVISTA BRASILEIRA DE REUMATOLOGIA

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SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Original article

Metabolic syndrome in patients with rheumatoid arthritis followed at a University Hospital in Northeastern Brazil

Brenda Maria Gurgel Barreto de Oliveira[a], *Marta Maria das Chagas Medeiros*[b,*], *João Victor Medeiros de Cerqueira*[c], *Raquel Telles de Souza Quixadá*[a], *Ídila Mont'Alverne Xavier de Oliveira*[a]

[a] *Hospital Universitário Walter Cantídio (HUWC), Universidade Federal do Ceará (UFC), Fortaleza, CE, Brazil*
[b] *Medicine School, Universidade Federal do Ceará (UFC), Fortaleza, CE, Brazil*
[c] *Medical Course, Universidade de Fortaleza (UNIFOR), Fortaleza, CE, Brazil*

ARTICLE INFO

Article history:
Received 29 January 2014
Accepted 29 May 2015
Available online 12 September 2015

Keywords:
Metabolic syndrome
Rheumatoid arthritis
Cardiovascular diseases

ABSTRACT

Introduction: Patients with rheumatoid arthritis (RA) are 30–60% more likely to develop cardiovascular disease (CV) than the general population. Metabolic syndrome (MS), defined by a number of cardiovascular risk factors, confers a greater risk of CVdisease and diabetes. The association of MS with RA is not yet fully understood and its prevalence varies from 19 to 63% across studies.

Objectives: To assess the prevalence of MS in a population of RA patients followed in a hospital in Northeastern Brazil and analyze associations of demographic and clinical factors with MS.

Methods: Outpatients with RA were evaluated in a cross-sectional study regarding demographic, clinical, laboratory and anthropometric data. The criteria for defining MS were those adopted by NCEPIII (2005) and IDF (2006).

Results: 110 patients with RA were studied; 97.3% were female, with a mean age of 55.5 years (SD = 12.9) and duration of illness of 11.2 years (SD = 7.3). The MS prevalence from NCEPIII (2005) and IDF (2005) were, respectively, 50% and 53.4%. Advanced age (57.9 ± 11.9 *versus* 52.9 ± 13.5; $p = 0.04$) and smoking load >20 packs/year (29% *versus* 9%, $p = 0.008$) were associated with MS. The major components of the metabolic syndrome were abdominal obesity (98.1%), hypertension (80%) and low HDL cholesterol (72.2%).

Conclusions: RA patients in a tertiary center in Northeastern Brazil showed high prevalence of MS. It is worth noting that almost all patients had MS and abdominal obesity, which has important practical implications. In addition to the components of MS, age and smoking were associated with this syndrome.

* *Corresponding author.*
E-mail: mmcmedeiros@hotmail.com (M.M.C. Medeiros).
http://dx.doi.org/10.1016/j.rbre.2015.08.016

Síndrome metabólica em pacientes com diagnóstico de artrite reumatoide acompanhados em um Hospital Universitário do Nordeste brasileiro

Palavras-chave:
Síndrome metabólica
Artrite reumatoide
Doenças cardiovasculares

RESUMO

Introdução: Pacientes com artrite reumatoide (AR) têm 30 a 60% mais chances de desenvolver doenças cardiovasculares (DCV) do que a população geral. A síndrome metabólica (SM), definida por um conjunto de fatores de risco cardiovasculares, confere maior risco de DCV e diabete. A associação da SM com AR ainda não está totalmente esclarecida e sua prevalência varia de 19 a 63% entre os estudos.

Objetivos: Avaliar a prevalência de SM numa população de pacientes com AR acompanhada num hospital do Nordeste brasileiro e analisar associações de fatores demográficos e clínicos com SM.

Métodos: Pacientes ambulatoriais com AR foram transversalmente avaliados com relação a dados demográficos, clínicos, laboratoriais e antropométricos. Os critérios para definir SM foram os adotados pelo NCEPIII (2005) e IDF (2006).

Resultados: Foram estudados 110 pacientes com AR, 97,3% mulheres com média de 55,5 anos (DP = 12,9) e duração da doença de 11,2 anos (DP = 7,3). As prevalências de SM do NCEPIII (2005) e IDF (2005) foram, respectivamente, 50% e 53,4%. Idade avançada (57,9 ± 11,9 *versus* 52,9 ± 13,5; $p = 0,04$) e carga tabágica > 20 maços ano (29% *versus* 9%; $p = 0,008$) estiveram associadas com SM. Os principais componentes da SM foram obesidade abdominal (98,1%), hipertensão arterial (80%) e HDL baixo (72,2%).

Conclusões: Pacientes com AR de um serviço terciário do Nordeste brasileiro apresentaram alta prevalência de SM. Chama atenção a quase totalidade dos pacientes com SM e obesidade abdominal, o que traz implicações práticas importantes. Além dos componentes de SM, idade e tabagismo se mostrarem associados com SM.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory, autoimmune, chronic disease which mainly affects peripheral joints. Recent epidemiological studies have suggested that RA is an independent risk factor for cardiovascular (CV) diseases, and RA patients are 30–60% more likely to develop (CV) diseases, that are characterized as the most important cause of morbidity and mortality in patients with RA.[1,2] The most likely explanation for this is the process of endothelial dysfunction and accelerated atherosclerosis that occur in these patients secondary to chronic inflammation and also to a higher prevalence of traditional cardiovascular risk factors. The presence of metabolic syndrome (MS), also known as insulin resistance syndrome, characterized by the combination of cardiovascular risk factors such as hypertension, obesity, high blood glucose, insulin resistance (IR) and dyslipidemia, confers a greater cardiovascular morbidity than the sum of the risks associated with each individual component.[3]

Its etiology remains elusive, but studies point to IR as the main mediator in the pathophysiology of MS. Multiple metabolic pathways have been proposed to connect IR and compensatory hyperinsulinemia to other metabolic risk factors.[4,5] Although the role of MS as a predictor of cardiovascular risk has been hotly debated, a meta-analysis of 2010 involving more than 950,000 patients concluded that MS increases twice the risk of (CV) diseases and 1.5 times the overall mortality, as well as an increase of five times for risk of occurrence of type 2 diabetes mellitus.[6] MS and IR have also been associated with several other diseases, such as hepatic steatosis, fibrosis and cirrhosis,[7] polycystic ovary syndrome,[8] cholelithiasis,[9] sleep apnea,[10] chronic kidney disease,[11] and gout.[12]

The prevalence of MS in patients with RA varies from 14% to 63%.[13–29] Some controlled cross-sectional studies have shown a higher prevalence in patients than in controls,[16,22,25,26,28] but other studies found no differences.[14,15,20,24,27] Epidemiological and methodological factors may justify such different results, for instance, the characteristics of the study population, origin of the patients, criteria used to define MS, and study design. However, evidence of accelerated atherosclerosis in patients with RA related to systemic inflammatory activity, together with the high prevalence of traditional cardiovascular risk factors in these patients, favor the increased risk of MS in patients with RA.[1,3,6,13–16] The approach to cardiovascular risk factors and MS in patients with RA is so important that in 2012 the Brazilian Society of Rheumatology proposed a consensus on the management of comorbidities in patients with RA, including an early identification and appropriate treatment of MS, besides other cardiovascular risk factors in all patients diagnosed with RA.[30]

The main aim of this study was to determine the prevalence of MS in a population of RA patients followed in a university hospital in Northeastern Brazil, and to analyze associations of demographic and clinical factors with the presence of MS.

Patients and methods

Patients diagnosed with RA according to the 1988 ACR criteria[31] and followed at the Rheumatology Center outpatient clinic, Hospital Universitário Walter Cantídio, Universidade Federal do Ceará, were sequentially invited to participate in this study. Patients with other autoimmune diseases, except secondary Sjogren's syndrome, were excluded. The study began in January 2013 and ended in December 2013 and the data collection was made with a cross-sectional design in the same period. A total of 110 patients was studied. Demographic (gender, age, race, education level) and clinical data related to RA (disease duration since diagnosis, the presence of extra-articular manifestations, rheumatoid factor, cyclic citrullinated peptide antibody [anti-CCP], medications used, bone erosions) and the presence of cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, heart disease, smoking) were collected from clinical records. Given that data on smoking are often not recorded properly in the clinical records, information about smoking was directly asked for the patient at the assessment day: never smoked, smoked in the past, currently smoking, number of cigarettes/day and smoking time. The patient was considered as a smoker if he/she had smoked or still was smoking for at least 6 months any number of cigarettes. Pack-years of smoking was calculated as the average number of cigarettes per day multiplied by years as a smoker, divided by 20. A history of >20 packs/year was considered as heavy smoking.[32] Information about dose and duration of prednisone use also were taken from the records and categorized as follows: no/very low exposure: daily use of prednisone <7.5 mg during <3 months; low exposure: daily use of prednisone <7.5 mg during >6 months; medium exposure: daily use of prednisone ≥7, 5–30 mg up for >6 months. Patients without any regular physical activity, or who performed sporadic physical activity (<150 min of activity/week), were classified as having a sedentary lifestyle.

During the physical examination, the number of swollen and tender joints was determined (28 joints) and patients were evaluated for the presence of joint deformities (reversible or irreversible). Measurements of blood pressure, weight, height and waist circumference were determined in the assessment day. Waist circumference was measured in centimeters with a tape at the midpoint between the lower part of the last rib and the iliac crest. Body Mass Index (BMI) was calculated using the formula weight over height squared. Disease activity was measured by the instrument Disease Activity Score 28 (DAS28)[33] also in the study visit day, always using the last ESR obtained. Functional capacity was assessed using the Health Assessment Questionnaire (HAQ),[34] with scores from 0 to 3: 0 meaning no loss of physical function, and 3 meaning complete physical disability. Recent laboratory data (blood count, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], fasting glucose, total cholesterol, high density lipoprotein [HDL] cholesterol, triglycerides, creatinine and urea) were also assessed.

MS criteria

There are five definitions for MS, all including dosages of HDL cholesterol, triglycerides, fasting glucose and blood pressure, and waist circumference measurement; and three of these include criteria for IR. These definitions also differ with respect to cutoff points in blood glucose, HDL, triglycerides and blood pressure levels and abdominal circumference measurement. The most widely used definitions are the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP ATP III)[35] and the International Diabetes Federation (IDF)[36]; therefore, we used these two definitions updated in 2005 and 2006, respectively, to calculate only the prevalence. To compare demographic and clinical factors between the group of patients with RA and MS *versus* patients with RA, but without MS, we used the MS rate calculated by NCEP ATP III.

The NCEP ATP III (2005) criteria requires three out of five factors to establish the diagnosis as follows: fasting glucose ≥100 mg/dL or use of hypoglycemic agents; HDL <40 mg/dL (men) or <50 mg/dL (women) or use of LDL lowering drugs; triglycerides ≥150 mg/dL or use of triglyceride-lowering medications; waist circumference ≥102 cm (men) or ≥88 cm (women); and blood pressure ≥130/85 mmHg or use of antihypertensive drugs. The criteria to consider MS according to IDF are: mandatory presence of abdominal circumference ≥94 cm (men) or ≥80 cm (women) and at least two of the other four criteria described above.

Statistical analysis was performed using Stata software version 9.0. For descriptive analysis of general characteristics of the sample, proportions and means ± standard deviations (SD) were calculated. Student's *t* test for independent samples was used to compare means between groups, and the chi-squared test was applied to compare proportions. The level of statistical significance set at 5% ($p < 0.05$) was used for all statistical tests. The study was approved by the Research Ethics Committee of the Hospital Universitário Walter Cantídio (HUWC) – Universidade Federal do Ceará (Protocol. N. 086.08.11).

Results

The general characteristics of the 110 patients studied are shown in Table 1. The mean age was 55.5 ± 12.9 years, and most of the subjects were female (107 women and 3 men), with low educational level (73.4%) and with the prevalence of Caucasian/brown subjects (53.2%). The mean disease duration was 11.2 ± 7.3 years. 84% of the results for rheumatoid factor were positive; and for anti-CCP 83.3% were positive (10 were positive in 12 patients). X-rays of hands and feet were obtained only from 55 patients of this sample, with 19 patients presenting joint erosions (34.5%). More than 90% of the patients were continuously taking oral prednisone at a mean dose of 5.06 ± 2.20 mg/day. With respect to synthetic disease-modifying drugs, the most used was methotrexate (95.5%), followed by leflunomide (71.2%). Anti-TNF-alpha agents were used by 31.8% of the patients. Disease activity

Table 1 – Characteristics of patients with rheumatoid arthritis followed at the Hospital Universitário Walter Cantidio-UFC (*n* = 110).

Feature	
Female gender, years (%)	97.3
Age (mean ± SD)	55.5 ± 12.9
Marital status (%)	
Single	33.3
Married	50.9
Separated/widower	15.8
Educational level (%)	
Illiterate/literate	33.0
Elementary school	40.4
High school	22.9
College	3.7
Race (%)	
Caucasian	22.4
Brown	30.8
Mulatto	40.2
African American	6.6
Disease duration, years (mean ± SD)	11.2 ± 7.3
Rheumatoid factor, positive (%)	84.0
Anti-CCP (%)	83.3 (10/12)
Presence of extra-articular manifestations (%)	11.8
Irreversible deformities (%)	35.3
Bone erosions in hand and/or foot X-rays (%)	34.5 (19/55)
Current use of oral prednisone (%)	90.9
Current prednisone dose, mg/day (mean ± SD)	5.06 ± 2.23
Disease-modifying drugs used (%)	
Chloroquine	59.1
Methotrexate	95.5
Sulfasalazine	15.5
Leflunomide	71.2
Anti-TNF (infliximab, adalimumab and/or etanercept)	31.8
Abatacept	0.9
Rituximab	1.8
Number of synthetic disease-modifying drugs (mean ± SD)	2.4 ± 0.9
Number of biological disease-modifying drugs (mean ± SD)	0.3 ± 0.6
Health Assessment Questionnaire (HAQ) (mean ± SD)	0.97 ± 0.69
Disease Activity Score 28 (DAS28) (mean ± SD)	3.97 ± 1.38
Menopause (%)	78
Metabolic syndrome prevalence (%)	
NCEP ATPIII	50.0
IDF	53.4
Hypertension (%)	56.3
Triglycerides >150 mg/dL (%)	38.3
Low HDL (<50 mg/dL in men and <40 mg/dL in women) (%)	47.2
Diabetes mellitus (%)	12.7
Abdominal obesity (%)	75.4
Smoking (%)	44.0
Smoking history >20 packs/year (%)	19.1
Sedentary lifestyle (%)	53.6

NCEP ATPIII 2005, Adult Treatment Panel III of the National Cholesterol Education Program; IDF 2005, International Diabetes Federation.

assessed by DAS28 at the time of evaluation was 3.97 ± 1.38, and functional capacity assessed by HAQ was 0.97 ± 0.69.

The prevalence of MS was 50% and 53.4% by NCEP ATP III and IDF definitions, respectively. When demographic and clinical characteristics of patients with and without MS were compared (according to NCEP ATP III), only age showed statistically significant difference, with older subjects in MS group (57.9 *versus* 52.9 years; $p = 0.04$). Cardiovascular risk factors (hypertension, low HDL, high triglycerides, glucose intolerance or diabetes mellitus, abdominal adiposity, obesity, smoking history >20 packs/year) were more frequent in patients with MS. There was no statistical difference for inflammatory markers (Table 2). No relationship was found between exposure to oral prednisone and presence of MS (Table 3).

The most frequent components of MS definition were abdominal adiposity (98.1%), hypertension (80%) and low HDL (72.2%). Hypertriglyceridemia and glucose intolerance/diabetes mellitus were present in 59.2% and 46.3%, respectively (Table 4).

Discussion

Although several studies on prevalence of MS in RA have already been performed worldwide, the frequency found varies from 14 to 63% among the various populations studied, not always the values found are higher than in controls, and the association of factors related to rheumatoid arthritis (disease activity, inflammatory markers, severity of the disease, treatment) with MS varies greatly in the literature.[14–16,18,23–27,29] A frequent explanation for these discrepancies is the use of different criteria for MS classification. However, even when observing studies that used the same criteria, the prevalence rates vary widely (Table 5). Therefore, it is likely that other factors related to the characteristics of the study population, including genetic, ethnic, cultural, demographic, socioeconomic and clinical factors, also influence the prevalence rates. Thus, studies conducted with different populations are critical to try to detect other factors more associated with MS specific of that population and, from this point, one could try to interfere on such factors, in addition to offering information to a better understanding of the pathophysiological relationship between the different components and other cardiovascular risk factors.

The majority of the patients seen in this study were female, with a mean age of 55.5 years, of low socioeconomic status, with long-standing disease, and moderate disease activity; the vast majority of subjects in this sample were in chronic use of low-dose prednisone, were methotrexate and/or leflunomide users, and 1/3 of them was in use of anti-TNF alpha agents. The prevalence of MS was about 50% when using NCEPIII (2005) criteria, and of 53.4% with IDF (2006) definitions. Both definitions require the presence of three out of five criteria, but the main difference is that IDF requires obesity (waist circumference ≥94 cm for men or ≥80 cm for women) as one of these three criteria, and the cutoff point to consider the presence of obesity is lower than that adopted in the NCEPIII definition (≥102 cm for men and ≥88 cm for women); the other four criteria are the same. For this reason, the MS rate by IDF definition is

Table 2 – Characteristics of rheumatoid arthritis patients followed at the Hospital Universitário Walter Cantídio-UFC according to the presence or absence of metabolic syndrome (NCEP III).

	Metabolic syndrome (+) ($n = 55$)	Metabolic syndrome (–) ($n = 55$)	p
Demographics			
Female gender (%)	100.0	94.5	0.07
Age, years (mean ± SD)	57.9 ± 11.9	52.9 ± 13.5	0.04
Caucasian/brown race (%)	52.7	56.4	0.82
Educational level ≥ high school (%)	25.5	27.3	0.83
Clinical features			
Disease duration, years (mean ± SD)	11.8 ± 7.2	10.5 ± 7.4	0.34
Rheumatoid factor (%)	84.9	83.0	0.79
Extra-articular manifestations (%)	9.0	14.5	0.30
Number of DMARDs (mean ± SD)	2.3 ± 0.8	2.5 ± 0.9	0.53
Current prednisone dose, mg/day (mean ± SD)	5.3 ± 2.1	4.8 ± 2.2	0.33
Methotrexate use (%)	94.5	96.3	0.64
Irreversible deformities (%)	35.2	24.5	0.22
Radiological erosions (%)	37.9	30.7	0.57
HAQ (mean ± SD)	1.07 ± 0.72	0.88 ± 0.65	0.17
DAS 28 (mean ± SD)	3.89 ± 1.38	4.05 ± 1.39	0.64
Cardiovascular risk factors			
Smoking history >20 packs/year (%)	29.0	9.0	0.008
Hypertension (%)	80.0	32.7	0.0001
Low HDL (%)	72.2	21.1	0.0001
Triglycerides >150 mg/dL (%)	59.2	16.9	0.0001
Diabetes mellitus/glucose intolerance (%)	46.3	16.7	0.001
Abdominal adiposity (%)	98.1	52.7	0.0001
BMI ≥ 30 kg/m^2 (%)	56.3	20	0.0001
Sedentary lifestyle (%)	56.4	50.9	0.56
Menopause (%)	83.3	72.0	0.09
Inflammatory markers			
CRP (mg/dL) (mean ± SD)	0.95 ± 1.3	0.87 ± 0.85	0.69
ESR (mean ± SD)	28.4 ± 20.5	30.9 ± 22.7	0.54

DMARDs, disease-modifying antirheumatic drugs; BMI, body mass index; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score; ESR, erythrocyte sedimentation rate.

almost always a little higher than 2005 NCEPIII's. With respect to demographic and clinical factors, only older age was associated with MS in this study. We found no association with disease duration, use of glucocorticoids, functional capacity and disease activity. What drew a lot of attention was the high prevalence of abdominal obesity in patients with MS (98.1%) and the association between heavy smoking story and MS.

The prevalence of MS in our study has been among the largest ever recorded in all studies (Table 5). Comparing only studies using the definition of NCEPIII, MS prevalence in RA among various international populations ranged from 19% to 55.5%. Also, considering only studies that included a control group, some did not find a relationship between MS and RA,[14,15,20,24] others have found increased MS,[16,22,25,26,28] and two studies showed higher rates in controls than in patients with RA.[21,29] The study by La Montagna et al.,[15] conducted at the University of Naples, Italy, with 45 patients and 48 controls (patients with myofascial pain, carpal tunnel syndrome and shoulder periarthritis), found a MS rate in RA similar to ours (55.5%). La Montagna's patients had clinical and demographic characteristics similar to those of our patients with regard to age, disease duration, gender and current dose of glucocorticoids. However, they also found a high prevalence of MS in controls (45.8%), with no statistical difference between the two groups. Although our study lacked a control

Table 3 – Exposure to oral corticosteroids (prednisone) in rheumatoid arthritis patients with metabolic syndrome (NCEP III) and without metabolic syndrome followed at the Hospital Universitário Walter Cantídio-UFC.

Corticosteroid dose	Patients with metabolic syndrome (n/%)	Patients without metabolic syndrome (n/%)
Not exposed, or very low exposure	4 (7.27%)	7 (12.96%)
Low exposure	44 (80%)	42 (77.78%)
Medium exposure	7 (12.73%)	5 (9.26%)

Table 4 – Metabolic syndrome (NCEP III) parameterspresent in patients with rheumatoid arthritis followed at the Hospital Universitário Walter Cantídio-UFC.

Metabolic syndrome component	Percentage (%)
Hypertension	80.0
Abdominal adiposity	98.1
Low HDL	72.2
High triglycerides	59.2
Fasting glycaemia ≥100 mg/dL and/or DM	46.3

Table 5 – Prevalence of metabolic syndrome in patients with rheumatoid arthritis according to several studies.

Author, year	Study design	Number of patients with RA/controls	Age, years (mean ± SD or median, IQR)	Disease duration, years (mean ± SD or median, IQR)	Prevalence of metabolic syndrome in RA (%)
Deissein et al., 2006	Cross-sectional	74	55.8 (53.2–58.3)	12.8 (12.3–15.2)	19% (NCEPIII 2005) 14% (WHO)
Karvounaris et al., 2007	Case–control	200/400	63 ± 11	9.3 ± 8.8	44% (NCEPIII 2001)
La Montagna et al., 2007	Case–control	45/48	53.8 ± 11.6	12.6 ± 8.2	55.5% (NCEPIII 2005)
Chung et al., 2008	Case–control	154/85	59 (52–67)	20 (14–24)	42% (NCEPIII 2001) 42% (WHO)
Zonana-Nacach et al., 2008	Cross-sectional	107	48 ± 12	11.2 ± 9.3	18.7% (NCEPIII 2001)
Toms et al., 2009	Cross-sectional	400	63.0 (55.4–69.2)	10 (4–18)	40.1% (NCEPIII 2005) 45.3% (IDF) 19.4% (WHO)
Elkan et al., 2009	Cross-sectional	80	61.4 ± 12	6 (2–15)	20% (women) (IDF) 63% (men) (IDF)
Giles et al., 2010	Case–control	131/121	61 ± 9	9 (5–17)	36% (NCEPIII 2005)
Sahebari et al., 2011	Case–control	120/500	45.5 ± 13	5.5 ± 5.2	30.8% (IDF) 45.2% (NCEPIII 2001)
Crowson et al., 2011	Case–control	232/1241	58.8 ± 12.8	7 (4.1–12.8)	33% (NCEPIII 2005)
Mok et al., 2011	Cross-sectional	699	53.3 ± 12	5.3 ± 5.4	20% (NCEPIII 2005)
Karimi et al., 2011	Case–control	92/96	48.3 ± 14.6	8 (5–14)	27.2% (NCEPIII 2001) 19.6% (WHO)
Da Cunha et al., 2012	Case–control	283/226	56.8 ± 12.3	11.1 (4.9–16)	39% (NCEPIII 2005)
Karakoc et al., 2012	Case–control	54/52	49.7 ± 11.1	7.6	42.6% (NCEPIII 2005)
Lee et al., 2013	Case–control	84/109	50.6 ± 11.3	3.5 (2.0–6.3)	19% (NCEPIII 2005)
Rostom et al., 2013	Case–control	120/100	49 ± 12	7.8	32.4% (NCEPIII 2005) 48.6% (IDF) 20% (WHO)
Salinas et al., 2013	Case–control	409/624	55.5 ± 13.2	8 (4–15)	30% (NCEPIII 2005) 35% (IDF)
Medeiros et al., 2014[a]	Cross-sectional	110	57.9 ± 11.9	11.8 ± 7.2	50% (NCEPIII 2005) 53.4% (IDF)

IQR, interquartile range.
[a] Current study.

group, a systematic review recently published (2013) on the prevalence of MS in the Brazilian adult population included 10 studies conducted in several Brazilian regions, showing a mean rate of 29.6% for MS.[37] The only study conducted in Northeastern Brazil was in a random population-based sample that consisted of 240 subjects aged 25–87 years in a town of the semi-arid region of Bahia, where an age-adjusted rate of 24.8% was found with the use of NCEPIII 2001 definitions (cutoff point for glucose >110 mg/dL, rather than 100 mg/dL by NCEPIII 2005). La Montagna et al.[15] found a higher prevalence of IR (88.9% *versus* 6.2%) and a higher number of cases of subclinical atherosclerosis (assessed by measuring common carotid artery intima and media thicknesses by ultrasound) in patients with RA. The study by Karvounaris et al.,[14] held in Greece with 200 patients with RA and a control group of subjects without RA or other chronic inflammatory diseases, found a MS rate (NCEPIII 2001) of 44% in RA patients and of 41% in controls, also without significant difference. An

interesting fact was observed in this study: a much higher proportion of controls with abdominal obesity (83% of controls *versus* 71% of patients) and hypertension (77.5% of controls *versus* 66% of patients) – features which may be related to dietary habits of this population. Glucocorticoids were used by less than 30% of patients and anti-TNF-alpha agents by about 40%. The little use of glucocorticoids and the considerable rate of biological users may have contributed to flatten the MS rate among patients, narrowing the gap between patient and control groups. Favorable effect of anti-TNF-alpha agents in IR in patients with RA has been documented.[38,39] With regard to corticosteroids, both cumulative dose and chronic corticosteroid use were associated with IR and subclinical atherosclerosis in the Italian study, and its authors believe that exposure to glucocorticoids may be the triggering factor for IR and atherosclerosis. In our study, we found no association between exposure to oral glucocorticoids and MS, but IR and subclinical atherosclerosis are earlier alterations than MS; furthermore, over 90% of our sample of patients with RA was in continued use of low-dose prednisone, making it difficult the demonstration of a statistically significant difference between groups, if in fact this difference occurred. Other studies also showed that the continuous use of corticosteroids is an independent predictor of IR and MS in patients with RA,[13,28] while other authors have found no such association.[18] It seems that, thanks to their systemic anti-inflammatory effect, short-term glucocorticoids could improve IR,[40,41] but the long-term side effects (dyslipidemia, hyperglycemia, hypertension, IR and abdominal obesity) could collectively contribute to an increase of insulin resistance and the development of MS and atherosclerosis.

An American study with 131 patients and 121 controls without RA showed MS rates of 36% in RA and 27% in controls, with no statistically significant difference.[20] Although BMI and waist circumference values were similar between groups, the quantification of visceral fat by abdominal CT was higher in male patients than in male controls, while subcutaneous fat was higher in female patients than in female controls. Furthermore, the authors found a more important association of visceral fat with cardiometabolic risk factors in patients with RA of both genders *versus* controls, even in the face of similar waist circumference values. This has important practical implications, because measures to reduce visceral fat (weight loss) appear to exert most impact in reducing cardiovascular risk in patients with RA than in the general population. In our study, the most frequent component of MS was abdominal obesity, found in almost all patients (98.1%); and BMI $\geq$30 kg/m^2, indicating body obesity, was also found in more than half of our patients with MS. These two findings characterize a population of overweight patients, that may be secondary to carbohydrate-based eating habits, characteristic of the Northeastern Brazil population, sedentary lifestyle (more than half of patients), and chronic use of glucocorticoids (90.9%). Nutritional guidance, an adequate physical activity program and a more rational use of glucocorticoids can contribute to decrease the cardiovascular risk in patients with RA.

Another study that did not find an increased prevalence of MS in RA was held in Iran with 92 female RA patients, and 96 healthy women, with rates of 27.2% in patients and 35.4% in controls.[24] The mean age of patients (48.3 $\pm$ 14.6 years) and the duration of illness (median: 8 years) were lower than our findings. An interesting finding of this study is that over 90% of patients were taking hydroxychloroquine. A multicenter study in Argentina published quite recently (2013) evaluated 409 patients with RA and 624 controls and found a protective effect of hydroxychloroquine in MS.[29] In the Argentinian study the control group consisted of patients without RA and diagnosed with other rheumatic diseases: osteoarthritis, low back pain, fibromyalgia. The prevalence of MS by NCEPIII (2005) criteria was of 30% and 39% for patients and controls, respectively, with no statistically significant difference. Perhaps the patient characteristics in the control group caused an increase in the MS rate for this group, narrowing the gap between this group and RA patients' group. The only other factors associated with MS in this study were age and rheumatoid factor and anti-CCP positivity. Lee et al.[27] from Korea reported the lowest prevalence of MS in both AR and control groups (19% and 15.6%), with 84 cases and 109 healthy controls, all female. These patients presented an earlier disease (median: 3.5 years) and were younger (50.6 $\pm$ 11.3 years). In addition to these demographic factors, genetic and cultural characteristics and factors related to dietary habits specific of this population may have contributed to such low MS rate. In the Korean study, RA patients had abdominal obesity (29.8%) and hypertension (44%) rates lower than in our study.

The first study showing an increase of MS in RA was conducted at the University of Tennessee, USA, and published in 2008 with 154 patients and 85 controls (without chronic inflammatory disease).[16] Using NCEPIII 2001 definition, 42% of patients with long-standing RA (median: 20 years), 30% of patients with early RA (median: 2 years) and 22% of controls had MS. Compared to the present study, a higher proportion of male patients was included in the Tennessee study (27% *versus* 2.7%), the subjects had a higher level of education, and there had more Caucasian patients (~90% *versus* 22.4%). These factors may explain, in part, an MS rate slightly lower than that found in our study. Also in that study, the authors demonstrated a protective effect of hydroxychloroquine. In 2011, another American study by Crowson et al.[22] was published. This study recruited 232 cases and 1241 controls (patients without RA), showing 33% and 25% for MS, respectively. The authors believe that the exclusion of patients with previous cardiovascular disease may have decreased the actual prevalence of MS in their patients. Two other studies in Turkey[26] and Morocco[28] showed prevalence rates of 42.6% and 32.4%, respectively, with statistically significant differences compared to controls. In both studies, patients were younger and had less-lengthy disease, compared to our patients. High ESR and glucocorticoid use were associated with MS in the Moroccan study.

A Brazilian study by Cunha et al. conducted in the city of Porto Alegre and recently published (2012) included 283 RA patients and 226 healthy controls. In this study a higher rate of MS in patients *versus* controls (39% *versus* 19.5%) was found.[25] The means of age and disease duration were similar to those in our study, but the proportion of male patients was higher in Cunha's study (17.7% *versus* 2.7%). Cases and controls exhibited similar prevalence of obesity. In patients with RA, MS was associated with older age, lower educational level,

disease activity and a worst HAQ score. Older age has been associated with presence of MS in several studies, as well as in our study. A likely explanation for this is the increased chance of developing factors related to MS with the progression of age. Disease duration, presence of rheumatoid factor, extra-articular manifestations, smoking history ≥20 packs/year, use of glucocorticoids, antimalarials or methotrexate and inflammatory markers were not associated with MS in the study by Cunha et al.[25] An association between inflammatory activity and MS has been found by some authors,[14,16,23,27] but not by others.[21,24,26,29] Inflammatory cytokines present in RA, especially TNF-alpha and IL-6, increase IR, which promotes hyperglycemia, compensatory hyperinsulinemia and dyslipidemia,[23] favoring a higher risk for developing MS. The controversial association between inflammatory activity of RA and MS can be explained by the instruments used in studies to assess inflammation. Both the Disease Activity Score (DAS28) and serological inflammatory markers (ESR, CRP) evaluate time-point activity, not activity over time.

Cross-sectional studies have shown MS prevalence in RA ranging from 17% to 40.1% by NCEPIII criteria.[13,17–19,23] A UK study by Toms et al.[18] examined the relationship of exposure to glucocorticoids with MS, categorizing the exposure in "no exposure", "low exposure" (<7.5 mg/day for >6 months), or "medium exposure" (7.5–30 mg/day for >6 months), similar to our study. Neither the authors' nor the present study found any association of corticosteroid use with MS. In the Mexican study by Zonana-Nacach et al.[17] evaluating MS in patients with RA and systemic lupus erythematous, the frequency of MS was 18.7% and 16.7%, respectively. The variables associated with MS were older age, educational level, monthly income and smoking. In our study, we found an association between smoking history >20 packs/year and MS. The association between smoking and MS is not fully understood. Although there are several studies showing an association, especially in males,[42] the presence of other factors related to smokers' lifestyle could explain this association. For example, sedentary lifestyle and alcoholism are admittedly more common among smokers and could act as confounding variables.[43]

This study has some limitations. The lack of a control group without RA precludes a comparison of MS prevalence among RA patients and individuals without the disease in this population. Thus, while a prevalence of 50% in patients may seem high, one cannot say that MS occurs more often in RA patients than in people without RA. MS prevalence studies in an adult Brazilian population by other authors[37] make us believe that the rate found in the present study has been larger than in the general population (29.6%). However, genetic, cultural and nutritional characteristics specific of Brazilian regions should be considered, and perhaps the Brazilian rate is not a good reference of control for a Northeastern population. Another limitation of the study was related to sample size, which may have influenced the lack of statistical significance of some comparisons.

In summary, patients with a diagnosis of RA followed in a tertiary center of a university hospital in Northeastern Brazil present one of the highest prevalence rates of MS, when compared to studies in various parts of the world, including Brazil. Regarding the components of MS, it should be noticed the high proportion of patients with abdominal adiposity (98.1%), hypertension (80%) and low HDL (72.2%). Greater attention should be given to these patients regarding nutritional guidance and physical activity, in order to promote weight loss and a better control of metabolic changes. Heavy smoking was also significantly associated with MS in this study, but one cannot say that smoking is a risk factor for MS.

Conflicts of interest

The authors declare no conflicts of interest.

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