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Body composition evaluated by body mass index and bioelectrical impedance vectorial analysis in women with rheumatoid arthritis

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Data Analysis and Responsibility:

JAPJ, MLM was responsible for the conception and design of the study; generation, collection, and interpretation of data; and drafting the manuscript. LCM, CSD, LL, AOT were responsible for generation of data and revision of the manuscript. AHA, JAV, REM, MGC were responsible for analysis and interpretation of the data and revision of the manuscript. All authors approved the final version of the manuscript. The authors declare no conflicts of interest.

Highlights

1. Patients with rheumatoid arthritis with normal or high BMI have a significantly lower muscle component.
2. The frequency of cachexia detected by BIVA in patients with arthritis rheumatoid was higher
3. Lower phase angle could be an indicator of a worse prognosis during disease course in rheumatoid arthritis.
4. BIVA method in rheumatoid arthritis patients could be a suitable option for cachexia detection.

Abstract

Background: Rheumatoid arthritis (RA) is a complex inflammatory disease that modifies body composition. Although body mass index (BMI) is one of the clinical nutrition tools widely used to assess indirectly nutritional status, it is not able to identify these body alterations. Bioelectrical Vector Analysis (BIVA) is an alternative method to assess hydration and body cell mass of patients with wasting conditions. **Objective:** To investigate the differences in nutrition status according to BMI groups (normal, overweight and obesity) and BIVA classification (cachectic and non-cachectic) in women with RA. **Methods:** Women with confirmed diagnosis of RA were included from January 2015 to June 2016. Whole-body bioelectrical impedance was measured using a tetrapolar and mono-frequency equipment. Patients were classified according to BMI as: low body weight (n=6, 2.7%), normal (n=59, 26.3%), overweight (n=88, 39.3%) and obese (n=71, 31.7%), and each group was divided into BIVA groups (cachectic 51.8% and non-cachectic 48.2%). **Results:** A total of 224 RA patients were included, with mean age 52.7 years and median disease duration of 12 years. Significant differences were found in weight, arm circumference, waist, hip, resistance/height, reactance/height and erythrocyte sedimentation rate among all BMI groups. However, serum albumin levels were significantly different between cachectic and non-cachectic patients independently

of BMI. In all BMI categories, cachectic groups had lower reactance and phase angle than non-cachectic subjects. **Conclusion:** RA patients with normal or even high BMI have a significantly lower muscle component. Evaluation of body composition with BIVA in RA patients could be an option for cachexia detection.

Keywords: rheumatoid arthritis, bioelectrical impedance vector analysis, body mass index, body composition; nutritional status

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation, joint pain, and destruction of the synovial membranes [1]. Life expectancy of these patients can be reduced by an average of 3 to 18 years and 80% are disabled after 20 years [2, 3]. Metabolic alterations in RA due mainly to the liberation of tumor necrosis factor alpha and interleukin-1 beta can lead to rheumatoid cachexia, which is defined as “the involuntary loss of fat free mass (FFM) with minimal or not weight loss and increase or not of fat mass (FM)” which causes muscular weakness and loss of functional capacity. Also, the mean loss of FFM, present in almost two thirds of patients with RA, is between 13 and 15%. [4].

In clinical nutrition practice, a widely-employed tool used to evaluate body mass and hence nutritional status is the body mass index (BMI). However, its main limitation is that is not able to identify rheumatoid cachexia alterations such as loss of FFM and gain of FM [5].

Several imaging techniques have been used to analyze body composition in RA patients. Currently, the most useful tool for measuring soft tissue mass and bone mineral density is dual X-ray absorptiometry (DXA) [6, 7]. Nevertheless, DXA is not always accessible and is sensitive to the patient's hydration status [8] and also is associated with radiation exposure [9]. Therefore, a simple tool for identifying body composition alterations as rheumatoid cachexia in outpatient settings is necessary [10].

Bioelectrical impedance analysis (BIA) is easy to operate, portable, and has a relatively low cost. Additionally, it has been reported as one of the most commonly used methods to estimate body composition using prediction equations, taking into account impedance parameters and reactance [11, 12]. However, homogenous composition, fixed cross-sectional area and consistent distribution of current density are necessary assumptions for the correct estimation of body composition [12]. These conditions are frequently violated in sick and hospitalized patients since disturbed fluid status or altered distribution of extra- and intra-cellular water are often present [12]. For example, if an individual is hyperhydrated, the FFM value is overestimated [13].

Bioelectrical impedance vector analysis (BIVA or vector BIA) is an alternative method that overcomes the need of assumptions for conventional BIA because it determines the resistance (R) and the reactance (Xc) obtained at 50 kHz, which are normalized with the subject's height (R/H and Xc/H) and then plotted as random vectors (points) on the R-Xc graph (R/H in X axis and Xc/H in Y axis) [11, 12, 14]. Impedance vector of an individual patient can be plotted in confidence ellipses drawn from a healthy reference population; normal individuals fall within the reference 75% tolerance ellipse. Wasting conditions (e.g., cancer, heart failure, and anorexia nervosa) have been associated with a displacement downward and to the right along the minor axis in the middle regions of the RXc graph [11].

Evaluation of nutritional status by BIVA method in RA patients has not been reported in the literature. Therefore, the aim of the present study to investigate the differences in nutrition status according to BMI groups (normal, overweight and obesity) and BIVA classification (cachectic and non-cachectic) in women with RA.

Material and methods

Study population

A total of 224 patients with RA were consecutively recruited from January

2015 to June 2016 at two of the National Health Institutes in Mexico City, Mexico: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) and Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra (INR). All patients were ambulatory and attended at the Immunology and Rheumatology Clinic at their respective Institute. The study protocol was approved by the ethics and investigation in human's committee of both Institutes and an informed consent was obtained from all participants. Female patients, >18 years of age, with a confirmed diagnosis of RA according to the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) 2010 criteria were included [1]. Patients with end-stage renal disease, uncontrolled dysthyroidism, hepatic failure and cancer or other autoimmune disease overlapping were excluded to avoid confusion related to changes in body composition.

Three Rheumatologists (AHA, REM, MGC) blinded to the body composition data evaluated all patients. Information regarding comorbidities (e.g. arterial hypertension, diabetes mellitus and dyslipidemia), disease duration and treatment was obtained. Disease activity was assessed using the Disease Activity Score (DAS28) [15], a clinical index of RA disease activity that combines information from swollen joints, tender joints, as well as acute phase response and general health. According to this index, the level of disease activity is considered low (<3.2), moderate (3.2-5.1), or high (>5.1). Pain was evaluated with a Visual Analogue Scale (VAS), ranging from 1 to 10, while global functional status was assessed in classes I-IV. [16].

Venous blood samples were drawn from patients after an overnight fast for determination of high sensitive C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lymphocytes, hemoglobin, hematocrit and albumin. All laboratory tests were determined using routine automated analyzers. Serum albumin levels were determined using the bromocresol green albumin method.

Anthropometry

Weight and height were measured according to the standard anthropometric method [17], while body mass index (BMI) was calculated using the formula that divides the body weight in kilograms by the height squared in meters. Patients were classified as normal (18.5-24.9), overweight (25-29.9) or obesity (>30) [18]. A qualified Nutritionist (JAPJ, MLM, MOM) performed all measurements.

Bioelectrical impedance analysis (BIA)

Whole-body bioelectrical impedance was measured using a tetrapolar and mono-frequency equipment (RJL Quantum X, RJL Systems; Michigan, USA). All measurements were performed according to the reported technique [19]. Patients removed all metallic objects that were in contact with the skin to avoid erroneous measurements; they were in fasting conditions for at least 8 hours and avoided vigorous physical activities or alcohol intake in the previous 24-hours. During the procedure, patients were placed in decubitus position with arms apart 30 cm from the body and legs apart 50 cm from each another. In the case of obese patients (if necessary), a towel was placed between the thighs to avoid the contact and prevent poor conductivity. The impedance values were obtained at 50 kHz frequency: resistance (R), reactance (Xc) and the phase angle (PA). PA was obtained by a previous predictive formula [20].

Bioelectrical impedance vector analysis (BIVA)

The data obtained by BIA (R and Xc) were standardized in accordance with the height of each patient in order to obtain the impedance vector, which is represented in the RXc graph [11, 23]. The R-Xc graph used was the Mexican reference of healthy population [21-23].

The gender-specific RXc graph was divided into 2 sectors. Patients with vectors out of the 75% tolerance ellipse of the reference population at the right side of the RXc-graph were classified as cachectic and as overhydration those patients

with vectors below of the 75% tolerance ellipse of the reference population on the longitudinal axis of the RXc-graph. [21-24]

Statistical analysis

The Kolmogorov-Smirnov test was used to confirm if the data had a normal distribution. Continuous variables with normal distribution are presented as mean ± standard deviation, otherwise the data are presented as median and 25-75 percentiles. Categorical variables are presented as frequencies and percentages. The differences among the BMI groups (normal, overweight and obesity), and BIVA groups (cachectic and non-cachectic), were assessed using two-way analysis of covariance, with age as a covariable. Hotelling's T2 test was used to compare mean BIVA vectors of BMI groups divided by cachectic and non-cachectic subjects. A p value <0.05 was considered statistically significant. Analyses were performed using a commercially available package (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) and the BIVA Software 2002 (Piccoli A. and Pastori G., Department of Medical and Surgical Sciences, University of Padova, Padova, Italy, 2002).

Results

Two hundred and twenty four female patients with RA were included, with a mean age of 52.7 years and median disease duration of 12 years. The most frequent comorbidity was hypertension (27.3%), followed by dyslipidemia (14.1%) and diabetes (12.8%). Most of the patients had low disease activity (mean DAS28=3.1), and 37% were in functional class I. According to the VAS most patients had moderate pain (median VAS=6). The most frequent disease-modifying antirheumatic drugs were methotrexate (63.4%), sulfasalazine (33.5%), and antimalarials (30.8%), while glucocorticoids were used in 22.7% and leflunomide in 12.3%. These data are summarized in Table 1.

According to BMI groups, six patients (2.7%) had low body weight (not included in the analysis of Table 2); 59 (26.3%) were normal; 88 (39.3%) had overweight and 71 (31.7) had obesity. In accordance to BIVA, 116 (51.8%) were classified as cachectic and non-cachectic 108 (48.2%); and 47 (21%) with overhydration.

Table 2 shows comparisons of anthropometric, parameters of bioelectrical impedance analysis, albumin, CRP and ESR parameters between BMI categories divided by cachectic and non-cachectic subjects. Statistically significant differences were found in weight, arm, waist and hip circumferences, R/H and Xc/H between all BMI groups. In all BMI categories, cachectic groups had lower reactance and phase angle than non-cachectic subjects. When we compared the cachectic and non-cachectic group within each BMI category, we observed significant differences in arm circumference, R/H, Xc/H, phase angle and albumin levels. All cachectic subjects independently of BMI group had lower levels of serum albumin.

Figure 1 shows mean R/H and XC/H, where the values between non-cachectic subjects (1, 3 and 5) are very similar. However, mean R/H was higher in the cachectic groups of normal (2) and overweight BMI (4) while the cachectic group of obese BMI (6) showed lower R/H in comparison with the other two cachectic groups. In all BMI categories, cachectic groups had lower Xc/H and phase angle than each one of their non-cachectic counterparts, being all the differences statistically significant.

Discussion

In the present study, we observed that although patients were classified as normal, overweight or obese according to their BMI, BIVA detected cachectic patients within all BMI categories. In addition, serum albumin levels were lower in cachectic subjects independently of BMI categories; this could be explained because hypoalbuminemia is a consequence of inflammation due to suppression of albumin synthesis and transfer of albumin from the vascular to the extravascular space. Moreover, patients with RA have increased whole-body protein breakdown

associated with higher TNF-α levels. It has been reported that in patients with RA, serum albumin is lower than in controls, and statistically associated with RA functional class, while a negative correlation exists with clinical, functional, and laboratory markers of disease activity [25].

Our results are similar to previous descriptions. Van Bokhorst-de van der Schueren et al reported high prevalence of overweight and obesity in RA patients, in combination with a reduced FFM and an increase of the FM. This explains why despite their classification as normal weight, overweight or obese, cachectic patients can be detected by the BIVA method [26].

Elkan et al evaluated body composition by DXA and found that 52% of women and 30% of men with RA were malnourished according to FFM determined by this method even if they were classified as normal, overweight or obese by BMI. Thus, the authors concluded that neither the BMI nor the nutritional assessment and screening tools could detect the low FFM with sufficient sensitivity and specificity to be used to assess cachexia [27]. Also, Konijn et al studied the differences between BMI and BIA and found that 44% of the studied women with a normal BMI had low FFM and 75% of men and 40% women had high FM. [5] These results are similar to our findings, demonstrating the low value of the BMI measurement in RA patients [27] because is only able to reflect abundance of adipose tissue in very high BMI or a reduction of fat and lean mass in very low BMIs. The problem of sarcopenic obesity, which can occur in RA, is most certainly not reflected by the BMI.

The phase angle (PA) is the most widely used BIA impedance parameter [31], has been suggested to be an indicator of cellular health, where higher values reflect higher cellularity, cell membrane integrity and better cell function. PA correlates with nutritional status and it has shown to be highly predictive of impaired clinical outcome and mortality in a variety of diseases [12]. PA expresses changes in the quantity and quality of soft tissue mass [28]. There are, to our knowledge, no previous studies regarding PA in patients with RA. However, there is evidence that it is related with nutritional status, disease progression and patient prognosis in

heart failure patients. [29]. Considering that heart failure is characterized by a state of chronic inflammation and a hypercatabolic state, similar to RA, [30] we could hypothesize that lower PA in the cachectic patients is an indicator of a worse prognosis during disease course in RA.

Our study has certain limitations. First, patients had longstanding disease (median of 12 years), which could lead to a higher prevalence of cachexia. Studying patients with recent-onset RA and over time could be of interest to clarify the effect of disease duration on body composition. Second, the effect of the treatment on body composition could not be evaluated in the present study. The beneficial properties of antimalarials on metabolism are well known (reduced incidence of diabetes, reduced serum glucose, improved lipid profile and attenuation in atherosclerosis progression). Third, although patients with RA are treated with low doses of steroids, 23% of our population was receiving them and this should be considered due to the long-term effects of these compounds on fat mass.

In conclusion, RA patients with normal or even high BMI have a significantly lower muscle component. Evaluation of nutritional status with BIVA in RA patients could be a suitable option for cachexia detection and provide early intervention to improve body composition.

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Conflict of interest

All authors state no conflict of interest

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Table 1. Select characteristics of study population

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Variable	**n=224**
Age (years)	52.7 ± 14.2
Disease duration (years)	12 (6-19)
Body Mass Index (kg/m^2)	27.5± 4.8
DAS28	3.1 ± 1.4
Pain (VAS)	6 (3.2-8.0)
CRP (mg/dL)	1.9 (0.5-6.9)
ESR (mm/hr)	24.5 (13-36)
Lymphocytes (%)	22.4 ± 10
Albumin (g/dL)	4.0 ± 0.5
Hemoglobin (g/dL)	13.7 (12.7-14.6)
Hematocrit (%)	41 (38.2-43.7)
Hypertension, n (%)	62 (27.3)
Diabetes, n (%)	29 (12.8)
Dyslipidemia, n (%)	32 (14.1)
Methotrexate, n (%)	144 (63.4)
Sulfasalazine, n (%)	76 (33.5)
Antimalarials, n (%)	69 (30.8)
Glucocorticoids, n (%)	51 (22.7)
Leflunomide, n (%)	28 (12.3)

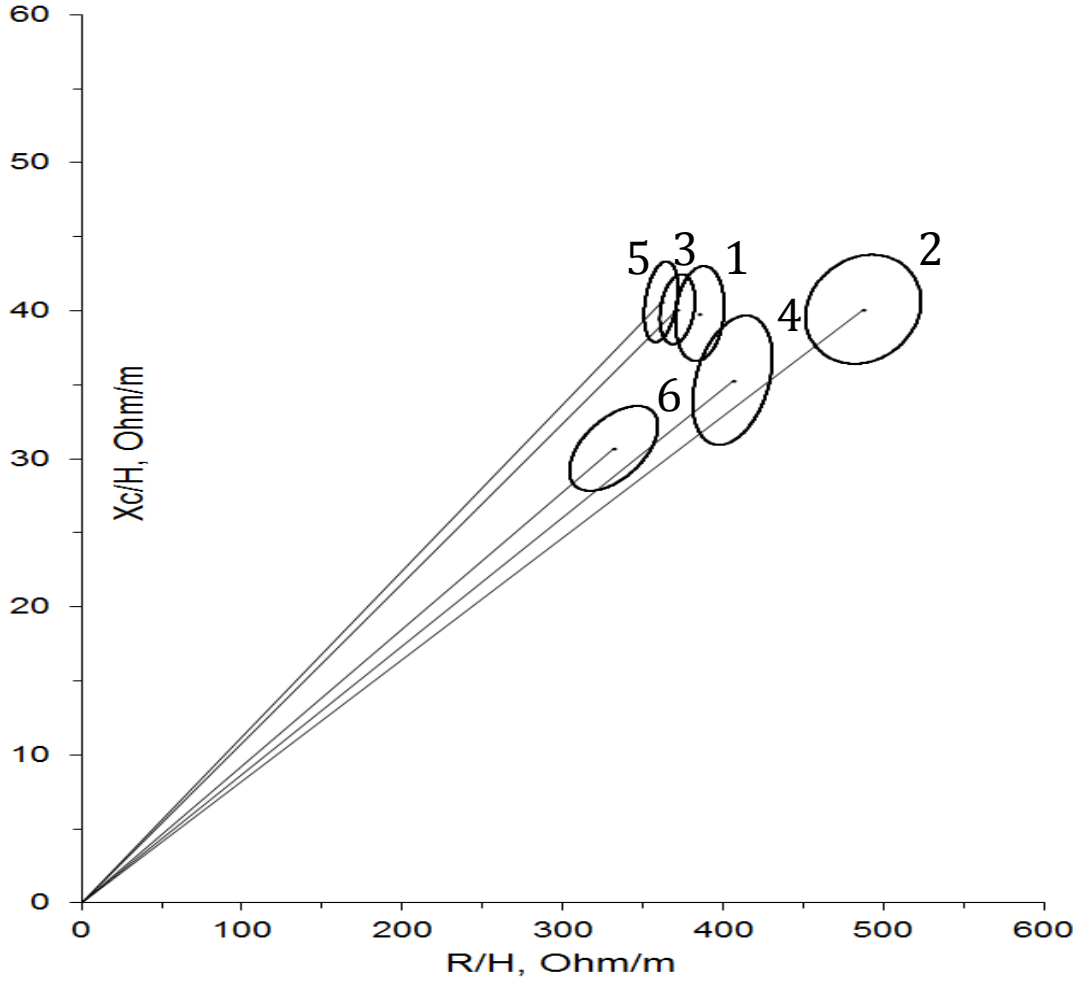
DAS: disease activity score, VAS: visual analogue scale, ACR: American College of Rheumatology, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate. Categorical variables are presented as absolute and relative frequencies and continuous variables are presented as mean ± standard deviation or median (p25 - p75).

Table 2. Body mass index classification according to rheumatoid cachexia

Variable	Body Mass Index Classification							
	Normal		Overweight		Obese			
	Non-cachectic n=23	Cachectic n=36	Non-Cachectic n=48	Cachectic n=40	Non-Cachectic n=37	Cachectic n=34	p between cachectic and non-cachectic	p between BMI classification
Age (years)	47.5 ± 13.8	55.3 ± 17.6	50 ± 14.2	56.3 ± 13.6	51.1 ± 11.4	55.9 ± 11.6	0.53	0.57
Anthropometric								
Weight (Kg)	57.4 ± 4.3	50.1 ± 7.3	65.2 ± 6.3	63.9 ± 7.0	74.5 ± 5.3	79.5 ± 10.6	0.8	<0.0001*
Arm Circumference (cm)	27.4 ± 1.4	24.8 ± 2	28.9 ± 2.7	27.7 ± 2.1	32.5 ± 1.9	32.8 ± 3.7	0.005	<0.0001
Waist (cm)	81.5 ± 11.4	78.1 ± 7.2	89.7 ± 5.5	87.8 ± 7.2	99.7 ± 5.7	103.6 ± 10.4	0.9	<0.0001
Hip (cm)	96.1 ± 3.7	92.8 ± 5.7	101.9 ± 5.1	101.7 ± 5.3	109 ± 5.8	114.5 ± 10.2	0.4	<0.0001
Bioimpedance parameters								
R/H	382.5 ± 30.7	474.2 ± 86.8	369.5 ± 33	398.5 ± 63.6	364.5 ± 27.5	326.4 ± 59.4	0.001	<0.0001*
Xc/H	39.6 ± 5.8	39 ± 8.9	40.0 ± 6.5	35.0 ± 10.4	41 ± 6.4	29 ± 4.9	<0.0001	0.02
Phase Angle (°)	5.9 ± 0.8	4.8 ± 1.1	6.2 ± 1.0	5.1 ± 1.4	6.4 ± 0.9	5.3 ± 1.1	<0.001	0.012
Biochemical								
Albumin (g/dL)	4.2 ± 0.3	3.7 ± 0.6	4.2 ± 0.2	3.8 ± 0.6	4.1 ± 0.4	3.9 ± 0.3	0.008	0.7
CRP (mg/dL)	1.1 (0.4 – 4.4)	1.5 (0.8 – 3.3)	1.4 (0.3 – 4.7)	1.1 (0.1 – 4.6)	2.1 (0.4 – 6.9)	0.9 (0.3 – 8)	0.56	0.76
ESR (mm/H)	26 (12.5 – 37.5)	22 (11 – 36)	20.5 (10 – 30.2)	34 (28 – 53)	26 (13 – 35)	25.5 (15 – 42)	0.21	0.83

R/H: resistance/height, Xc/H: reactance/height, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate; continuous variables are presented as mean ± standard deviation; *p<0.05 for interaction

Figure 1. Mean R/H and XC/H of BMI categories and the presence or not of cachexia



Group	Hotelling´s T^2 Test	Mahalonobis D	p
Normal BMI non-cachectic (1) vs Normal BMI cachectic (2)	32.8	1.53	<0.00001
Overweight BMI non-cachectic (3) vs Overweight BMI cachectic (4)	27.1	1.11	<0.00001
Obese BMI non-cachectic (5) vs Obese BMI cachectic (6)	42.4	1.55	<0.00001

Abbreviations. BMI: body mass index