Cachexia measured by bioelectrical impedance vector analysis and risk of infection in women with rheumatoid arthritis

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Received: 15 August 2022 / Revised: 28 October 2022 / Accepted: 31 October 2022 / Published online: 14 November 2022
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Abstract
Rheumatoid arthritis (RA) patients have a higher frequency of infections than the healthy population. The reason has yet to be explained but involves several factors, of which body composition and rheumatoid cachexia are often overlooked. This study aimed to evaluate whether patients with cachexia, measured by bioelectrical impedance vector analysis, are at an increased risk of developing infections compared with patients without cachexia. A secondary analysis of 186 women with RA enrolled in a randomized trial (ClinicalTrials.gov ID: NCT02900898, September 14, 2016) was completed. Medical records and phone calls were used to record infectious events diagnosed and treated during follow-up. Hazard ratios were calculated using Cox proportional hazard regression analysis, and a predictive model of infection was created. After 36 months of follow-up, 62 patients (26.7% non-cachectic and 44.3% cachectic, \( p < 0.01 \)) developed at least one infectious event. The most common site of infection was the urinary tract, followed by the lungs and respiratory tract. The presence of cachexia (HR 1.90, 95% CI 1.15–3.13) and the use of glucocorticoids (HR 1.77, 95% CI 1.01–3.09) were associated with infection in univariate and multivariate models. Body mass index (BMI), smoking, and methotrexate use were not associated with a higher frequency of infections. The presence of cachexia and the use of glucocorticoids were identified as predictors of infections in a cohort of female RA patients. More extensive measurements of body composition should be performed beyond BMI in RA patients to better understand its impact and to prevent additional comorbidities and complications.

Key Points
- The presence of cachexia measured by bioelectrical impedance vector analysis was associated with infectious events in women with rheumatoid arthritis, whereas body mass index did not show an association.
- Glucocorticoids were the only drug associated with a higher frequency of infection. None of the disease-modifying antirheumatic drugs, including methotrexate, showed an association.

Keywords  Bioelectrical impedance vector analysis · Body composition · Infection · Rheumatoid cachexia

Introduction
The frequency of infections in rheumatoid arthritis (RA) patients is higher than that in the healthy population [1]. Cohort studies have found the most common infection types in these patients are urinary tract infections, pneumonia, and skin/soft tissue [2]. Alongside this higher risk of infection, the overall mortality rate of patients with RA is higher than in the general population [3]. The mechanism that causes this higher risk is unclear, although it may be attributed to the altered immunological function of the disease itself, disability, interventions, and use of glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) [4].
A frequent condition in RA patients is cachexia, which is a multifactorial syndrome characterized by severe loss of body weight, fat, and muscle, and increased protein catabolism due to underlying disease(s) [5]. This condition is so common in RA patients that the term rheumatoid cachexia is used [6]. It is primarily caused by elevated resting energy expenditure as a consequence of excess inflammatory cytokine production and low physical activity [7]. Different studies have reported a rheumatoid cachexia prevalence of 15–32% [8]; however, currently, there is no agreement regarding clinical criteria for its diagnosis [9].

The most basic technique used to evaluate body composition is body mass index (BMI), which fails to identify the abundance or reduction of lean mass, allowing the condition to often go unrecognized in clinical practice [7, 10]. The gold standard for assessing body composition and cachexia is whole-body dual-energy X-ray absorptiometry, but for practicality and affordability reasons, bioelectrical impedance analysis (BIA) is most often used [11]. However, BIA uses regression models associated with gold standard techniques, hydration, and homogeneous body assumptions that in some populations can be erroneous. Taking BIA as its foundation, bioelectrical impedance vector analysis (BIVA) overcomes the need for assumptions, as it does not use mathematical models to estimate body compartments. It instead evaluates hydration and body cell mass by expressing the impedance vector in a graph of the reference population [12]. BIVA has been used to assess cachexia in patients with systemic lupus erythematosus, kidney failure, and RA [12, 13].

This study aimed to evaluate whether patients with cachexia measured by BIVA (BIVA-cachexia) are at an increased risk of developing infections in comparison with non-BIVA-cachectic patients.

Materials and methods

The present study was a secondary analysis performed between February 2019 and February 2020 of a registered clinical trial (ClinicalTrials.gov Identifier: NCT02900898, September 14, 2016). The rationale for the trial design, details, and eligibility features, as well as the main results, has been published previously [14]. Briefly, women > 18 years old with confirmed RA diagnosis were recruited during ambulatory visits at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary care center in Mexico City. Patients with end-stage renal disease, hepatic failure, cancer, or another autoimmune disease that overlapped were excluded to avoid confusion with changes in body composition. The original study aimed to assess the effects of a dynamic exercise program (DEP) in combination with a Mediterranean diet (MD) in women with RA and comprised three intervention groups (MD + DEP, MD, DEP) and one control group [14].

Anthropometric measurements were performed according to the reference manual for anthropometric standardization [15]. Body composition was estimated by BIVA using multifrequency BIA equipment (QuadScan 4000, BodyStat). To perform the BIA, participants emptied their bladder and removed any metal objects in direct contact with their skin; also, they were asked to withhold from eating, drinking, and exercising for 6 h, and to avoid alcohol ingestion and vigorous physical activities 24 h prior. Patients were placed in the decubitus position with arms on the side, 30 cm apart from their bodies, and legs 50 cm apart from each other. Four electrodes were placed on the dorsum of the right hand and foot after cleaning the area with rubbing alcohol. The impedance values (resistance (R), reactance (Xc), and phase angle) were obtained at a 50 kHz frequency, and these data were standardized to the height of each patient to obtain the impedance vector that was represented in the reference healthy Mexican women RXc graph [16]. Patients with vectors that fell outside of the 75% tolerance ellipse in the lower right quadrant (quadrant IV) were categorized as BIVA-cachectic.

Information regarding medical treatment, comorbidities, and clinical characteristics, including disease duration, functional class, disability index, and disease activity, was also obtained.

During a follow-up period of 36 months after the baseline evaluation, the electronic medical records were monitored and confirmatory phone calls were performed when necessary to assess the primary outcome of any infection diagnosed and treated during an outpatient consultation, an emergency room visit, or hospitalization.

To confirm if the data had a normal distribution, the Kolmogorov–Smirnov test was used. Continuous variables with a normal distribution are presented as the mean ± standard deviation; otherwise, as the median (25–75 percentiles). Categorical variables are presented as frequencies and percentages. Student’s t or Mann–Whitney U tests (continuous variables) and the $X^2$ test (qualitative variables) were used to find differences between BIVA-cachexia and non-BIVA-cachexia patients at the start of the study. Kaplan–Meier time-to-event curves and the log-rank test were generated to assess cumulative risk of infection according to the presence or absence of BIVA-cachexia. Cox multivariable regression analysis was used to evaluate the association between the incidence of infectious events and BIVA-cachexia. Variables with a p-value < 0.20 in the univariate analysis were included in the multivariate model.

Data analyses were performed using the SPSS Statistics software (IBM SPSS Statistics for Windows, Version 25) and the BIVA software 2002 (Piccoli A. and Pastori G.; Department of Medical and Surgical Sciences, University of Rome Tor Vergata, Rome, Italy).
of Padova, Padova, Italy, 2002). A \( p \)-value < 0.05 was considered statistically significant.

**Results**

Of the 223 women with RA originally considered eligible, 37 were excluded for not meeting the inclusion criteria \((n = 25)\) or declining to participate \((n = 12)\). The remaining 193 received a body composition measurement by BIVA at the baseline assessment. Seven of these 193 patients were lost to follow-up, and 186 were analyzed. Patients in the present analysis and the overall trial population were similar in characteristics and outcomes (data not shown). The median age was 48.1 ± 12.1 years, whereas the median disease duration was 12 (6–20) years. Overall disease activity was low, with a mean Disease Activity Score 28 (DAS28) of 2.6 ± 1.03.

Table 1 presents the comparison of clinical, anthropometric, and treatment characteristics between non BIVA-cachexia and BIVA-cachexia patients. No difference was found between groups regarding disease activity, age, the prevalence of comorbidities, or pharmacological treatment. Differences were found in all anthropometric and body composition variables, where the BIVA-cachexia group had lower weight, BMI, handgrip strength, and phase angle.

After the 36-month follow-up period, 62 patients presented at least one infection: 31 (26.7%) in the non BIVA-cachexia group and 31 (44.3%) in the cachectic group \((p < 0.01)\). A total of 94 infectious episodes were identified in these 62 patients, being the urinary tract infections the most frequent. Details of the sites of infections and the

**Table 1** Baseline characteristics of patients by study groups

| Variable                        | Non-BIVA-cachexia \((n = 116)\) | BIVA-cachexia \((n = 70)\) | \( p \)-value |
|---------------------------------|----------------------------------|-----------------------------|---------------|
| Demographic and clinical        |                                  |                             |               |
| Age (years)                     | 47 (38.2–56.0)                   | 53 (41.7–59.0)              | 0.07          |
| Disease duration (years)        | 10 (4–17)                        | 16 (8–25)                   | < 0.001       |
| DAS28                           | 2.5 ± 0.9                        | 2.7 ± 1.1                   | 0.42          |
| Functional class, \(n\) (%)     |                                  |                             |               |
| Class I                         | 90 (78.3)                        | 41 (59.4)                   | 0.01          |
| Class II                        | 22 (19.1)                        | 21 (30.4)                   | 0.89          |
| Class III                       | 3 (2.6)                          | 7 (10.1)                    | 0.47          |
| HAQ-DI                          | 0.75 (0.2–1.1)                   | 0.87 (0.37–1.5)             | 0.04          |
| Anthropometry and body composition |                                |                             |               |
| Weight (kg)                     | 64.4 (59.5–72.3)                 | 61.1 (55.4–68.0)            | < 0.001       |
| BMI (kg/m\(^2\))                | 27.9 ± 3.9                       | 26.6 ± 4.9                  | 0.04          |
| Handgrip strength (kg)          | 16.7 (13.7–23.0)                 | 11.0 (8.0–15.5)             | < 0.001       |
| Phase angle (°)                 | 5.4 (5.1–5.9)                    | 4.1 (3.6–4.6)               | < 0.001       |
| Comorbidities                   |                                  |                             |               |
| Arterial hypertension, \(n\) (%)| 20 (17.2)                        | 12 (17.1)                   | 0.98          |
| Hypothyroidism, \(n\) (%)       | 20 (17.2)                        | 13 (18.6)                   | 0.81          |
| Dyslipidemia, \(n\) (%)         | 19 (16.4)                        | 12 (17.2)                   | 0.89          |
| Diabetes mellitus, \(n\) (%)    | 11 (9.5)                         | 9 (12.9)                    | 0.47          |
| Smoking, \(n\) (%)              | 20 (17.2)                        | 11 (15.7)                   | 0.78          |
| Leukopenia, \(n\) (%)           | 10 (8.6)                         | 6 (8.5)                     | 0.98          |
| Treatment                       |                                  |                             |               |
| Chloroquine, \(n\) (%)          | 17 (14.9)                        | 7 (10)                      | 0.33          |
| Hydroxychloroquine, \(n\) (%)   | 35 (30.7)                        | 20 (28.6)                   | 0.75          |
| Glucocorticoids, \(n\) (%)      | 21 (18.1)                        | 13 (18.6)                   | 0.93          |
| Glucocorticoids (mg/day)        | 5.0 (2.5–5.0)                    | 5.0 (5.0–5.0)               | 0.38          |
| Methotrexate, \(n\) (%)         | 80 (69.0)                        | 45 (64.3)                   | 0.51          |
| Sulfasalazine, \(n\) (%)        | 27 (23.5)                        | 20 (28.6)                   | 0.44          |
| Leflunomide, \(n\) (%)          | 17 (14.9)                        | 17 (25.0)                   | 0.08          |
| Azathioprine, \(n\) (%)         | 2 (1.7)                          | 1 (1.4)                     | 0.87          |

Continuous variables are presented as the means (SD) and medians (p25–p75). Categorical variables are presented as absolute and relative frequencies.

DAS28, Disease Activity Score 28; HAQ-DI, Health Assessment Questionnaire Disability Index; BMI, body mass index.
| Table 2  Sites and causative agents of infectious events by BIVA-cachexia status |
|---------------------------------------------------------------|
| Causative agents by site of infection | Non-BIVA-cachexia \((n = 14)\) | BIVA-cachexia \((n = 17)\) |
|---------------------------------------------------------------|
| **Urinary tract \((n = 21)\)** | | |
| Bacterial \((n = 19)\) | | |
| *Escherichia coli*, \(n\) (%) | 9 (64.2) | 7 (38.8) |
| *Pseudomonas aeruginosa*, \(n\) (%) | 1 (7.1) | – |
| *Klebsiella pneumoniae*, \(n\) (%) | – | 1 (5.5) |
| *Raoultella ornithinolytica*, \(n\) (%) | – | 1 (5.5) |
| Fungal \((n = 2)\) | | |
| *Candida albicans*, \(n\) (%) | – | 2 (11.1) |
| **Pulmonary and upper respiratory tract \((n = 3)\)** | | |
| Bacterial \((n = 2)\) | | |
| *Staphylococcus aureus*, \(n\) (%) | 1 (7.1) | – |
| *Staphylococcus epidermis*, \(n\) (%) | – | 1 (5.5) |
| Mycobacterial \((n = 1)\) | | |
| *Mycobacterium tuberculosis*, \(n\) (%) | 1 (7.1) | – |
| **Post-operative, septic arthritis \((n = 3)\)** | | |
| Bacterial \((n = 2)\) | | |
| *Staphylococcus aureus*, \(n\) (%) | – | 1 (5.5) |
| *Staphylococcus hominis*, \(n\) (%) | – | 1 (5.5) |
| Fungal \((n = 1)\) | | |
| *Candida glabrata*, \(n\) (%) | 1 (7.1) | – |
| **Skin and soft tissue \((n = 2)\)** | | |
| Bacterial \((2)\) | | |
| *Staphylococcus lugdunensis*, \(n\) (%) | – | 1 (5.5) |
| *Bacteroides fragilis*, \(n\) (%) | – | 1 (5.5) |
| **Gastrointestinal \((n = 1)\)** | | |
| Bacterial \((n = 1)\) | | |
| *Clostridioides difficile*, \(n\) (%) | – | 1 (5.5) |
| **Genital \((n = 1)\)** | | |
| Bacterial \((n = 1)\) | | |
| *Gardnerella vaginalis*, \(n\) (%) | 1 (7.1) | – |

**Fig. 1** Kaplan–Meier survival curves at 36 months for any infectious event stratified by BIVA-cachexia status
causative agents according to BIVA-cachexia status are summarized in Table 2. Infections were responsible for mortality in three patients during the follow-up period: one with bacterial sepsis (non-BIVA-cachexia group), one secondary to septic arthritis (BIVA-cachexia group), and one as a consequence of pneumonia (BIVA-cachexia group).

In Fig. 1, we can see that the time-to-infection is lower in the BIVA-cachexia group compared with the non-BIVA-cachexia group (log-rank test, \( p < 0.01 \)). According to the Cox regression analysis, a total of six variables were independently associated with an infectious event, including BIVA-cachexia and the use of glucocorticoids. The coexistence of BIVA-cachexia and glucocorticoid use was associated with the incidence of infectious disease in this cohort of patients (Table 3). In a subanalysis, patients using a dose of prednisone of > 5 mg/day had a higher risk of infection than those using a dose of < 5 mg/day (HR 2.04, 95% CI 1.09–3.75).

Although this study was not designed to compare by body composition status change, a total of eleven patients changed their body composition status from non-BIVA-cachexia to BIVA-cachexia in a 6-month follow-up evaluation. Five of these eleven patients presented an infectious event.

### Discussion

This study allowed us to examine a possible association between cachexia and an increased risk of infection in women with RA.

A cohort study of infections in RA patients and healthy subjects found a HR of 1.45 (95% CI 1.29–1.64) when adjusted for sex, smoking status, leukopenia, glucocorticoid use, and diabetes mellitus [2]. Similar to the present study, the most frequent sites of infection included the urinary and respiratory tracts [2]. Also, age and the use of glucocorticoids were associated with infection in the univariate model, while methotrexate use and BMI were not. We differ, however, on smoking status and leukopenia. None of these two factors was associated with an increased risk, probably because the portion of smokers in our cohort was much smaller, as well as those with leukopenia [17].

A retrospective longitudinal study investigating the use of nonbiologic DMARDs and the risk of mild (required a physician visit) and serious infections (requiring hospitalization) concluded that the use of nonbiologic DMARDs alone did not increase the risk of infection, but the use of glucocorticoids did (RR 1.15, 95% CI 1.11–1.19). These findings are similar to ours [18]. Furthermore, glucocorticoids have been used for decades in the treatment of RA, as they can shift the cytokine response to suppress inflammation [19]. While their use cannot completely explain the increased risk of infection [2], RA patients who use long-term, stable low doses (10 mg/day) [20] had an increased risk of infection when using prednisone doses as low as 5 mg/day (HR 1.29, 95% CI 1.25–1.34) [21]. We found a similar result, where patients using prednisone doses of > 5 mg/day had a higher risk of infection than those using < 5 mg/day (HR 2.04, 95% CI 1.09–3.75).

It is difficult to pinpoint why cachexia increases the risk of infection in RA, considering that patients are exposed to additional risk factors. Cachexia affects muscle, the main source of glutamine, which is necessary for the cells of the immune system [22]. One study reported that low levels of plasma amino acids increased the risk of postoperative sepsis in sarcopenic patients. In univariate analyses, age (OR 1.08, 95% CI 1.02–1.14), sarcopenia (OR 1.93, 95% CI 1.72–8.77), and plasma glutamine levels < 580 nmol/mL

### Table 3

| Variables                  | Univariate analysis | Multivariate analysis |
|---------------------------|---------------------|-----------------------|
|                           | HR 95% CI           | p         | HR 95% CI | p     |
|                           | Lower | Upper |        | Lower | Upper |        |
| Age (years)               | 1.02  | 1.00  | 1.05  | 0.01  | 1.02  | 0.99  | 1.04  | 0.07  |
| Disease duration (years)  | 1.02  | 0.99  | 1.05  | 0.08  |        |        |        |       |
| Comorbidities (yes/no)    | 1.29  | 0.67  | 2.48  | 0.43  |        |        |        |       |
| BMI (kg/m²)               | 0.97  | 0.92  | 1.03  | 0.47  |        |        |        |       |
| Smoking (yes/no)          | 1.25  | 0.66  | 2.35  | 0.48  |        |        |        |       |
| Leukopenia (yes/no)       | 0.48  | 1.35  | 0.58  | 3.15  |        |        |        |       |
| BIVA-cachexia (yes/no)    | 1.90  | 1.15  | 3.13  | 0.01  | 1.84  | 1.11  | 3.07  | 0.01  |
| Phase angle (°)           | 0.72  | 0.57  | 0.91  | <0.01 |        |        |        |       |
| Glucocorticoids (yes/no)  | 1.77  | 1.01  | 3.09  | 0.04  | 1.81  | 1.01  | 3.24  | 0.04  |
| Methotrexate (yes/no)     | 0.68  | 0.41  | 1.14  | 0.15  | 0.71  | 0.42  | 1.22  | 0.22  |
| Randomized intervention   | 1.03  | 0.83  | 1.29  | 0.73  | 1.05  | 0.84  | 1.30  | 0.63  |

BMI, body mass index; BIVA, bioelectrical impedance vector analysis
A recent study on COVID-19 patients found that the explanatory variables for COVID-19 severity included increased BMI and plasma TRIM63, among others. According to these results, alterations in body composition are important in the prognosis. TRIM63 plasma levels were considered markers of muscle atrophy, which were found to increase with disease severity, with a significant difference ($p < 0.001$) between the medians of mild/moderate, severe, and critical COVID-19 [26]. Although a relatively new marker, recent studies have been performed to describe the mechanism and regulation of this enzyme, which is now known to have an important role in skeletal muscle atrophy [27].

Limitations of the present study are as follows: despite the best effort to include every infection the patients presented during the follow-up period, only episodes that required medical attention, were diagnosed, and prescribed treatment by a physician were included; therefore, the possibility of having missed infectious events may exist. All patients were distributed among the original study’s 4 intervention groups; however, we took this factor into account, and it did not present an association in the univariate or multivariate analyses (Table 3). Moreover, patients with BIVA-cachexia had longer disease duration, a worse functional class, and a higher disability index. Finally, all patients presented low disease activity and were treated with conventional DMARDs; therefore, the extrapolation of these results to patients with active disease, receiving biological DMARDs or small molecule inhibitors, is not possible.

In conclusion, the presence of cachexia measured by BIVA and the use of glucocorticoids were independent predictors of infections in female RA patients with low disease activity undergoing conventional pharmacological treatment. These results reinforce the idea that body composition should be routinely measured beyond BMI in RA patients to better understand its impact and to prevent additional comorbidities and complications.

Acknowledgements This work is part of the Ph.D. dissertation of Midori Ogata-Medel. She was also a Consejo Nacional de Ciencia y Tecnología (CONACYT) fellow (scholarship CVU number: 824831).

Funding The research leading to these results received funding from CONACyT through the Research Project Grant 000000000261652 and by sponsoring the scholarship of Midori Ogata Medel during her PhD course study. The sponsor did not have any role in study design, collection, analysis and interpretation of data, or in writing and submitting this paper for publication.

Compliance with ethical standards

Ethics approval and consent to participate This study was approved by the Institutional Human Ethics and Research Committees of the INCMNSZ and all involved individuals gave their informed consent before their inclusion.

Disclosures None.

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