Research Article

Risk for Sarcopenia, Inflammatory Mediators, and Disability in Elderly Women with Low Back Pain: BACE-Brazil

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Abstract

Objective: To compare pain, disability and plasma inflammatory mediators (tumor-necrosis-factor [TNF]-alpha, soluble-TNF-receptor-1 [sTNF-R1], interleukin [IL]-1β, IL-6) between elderly women with acute low back pain (LBP) "at risk" or "without risk" for sarcopenia.

Subjects and methods: 155 women, from the "International Back Complaints in the Elders" study, were divided into groups: "without sarcopenia" and "at risk for sarcopenia". Inflammatory mediators were measured using enzyme-linked-immunosorbent-assays; Disability, using Roland-Morris Disability Questionnaire; and Pain, using McGill-Pain Questionnaire, Numerical Pain Scale, and frequency.

Results and conclusions: 52.26% elderly women were "at risk" for sarcopenia and had higher levels of sTNF-R1 (p=0.037), greater LBP severity (p=0.043), frequency (p=0.037) and disability (p=0.011) than those without risk for sarcopenia.

ABBREVIATIONS

TNF: Tumor-Necrosis-Factor, sTNF-R1: Soluble-TNF-Receptor-1; IL: Interleukin; LBP: Low Back Pain

INTRODUCTION

The European Working Group on Sarcopenia in Older People (EWGSOP) [1] recognizes sarcopenia as a geriatric syndrome that is characterized by progressive and generalized loss of skeletal muscle mass and strength. It is associated with risk of adverse outcomes such as physical disability, poor quality of life, and death [1]. There are several mechanisms that may be involved in the onset and progression of sarcopenia, and these are related to an imbalance between anabolic and catabolic factors [2]. Besides, it is still unclear the relationship between the amount of loss of strength and muscle mass. Some evidence indicates that this relationship is not linear, given that the loss of muscle strength precede the decrease of muscle mass, and particularly the changes in strength appears to be most predictive of adverse health effects [3].

Inflammatory mediators are known to increase in level as individual’s age, which is characterized by chronic, subclinical inflammation known as “inflammaging” [4]. Pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, are recognized as causes of muscular catabolism [5], and increases in their levels have been associated with loss of muscle strength, functional capacity, low socioeconomic levels, and a poor lifestyle in older adults [4,6].

Cytokines have also been associated with pain [7-9]. Low back pain (LBP) is an important complaint among the elderly because it has a significant impact on function. LBP is defined as pain, tension, or rigidity localized in the region between the inferior ribs and the gluteal line [10].

Pain may represent one of many age-related factors that contribute to the progression of sarcopenia. Increased IL-6 and TNF-α levels were detected by assessing local tissue in adults with LBP. Neural compression [7], disc herniation [8], and facet degeneration [9] were positively correlated with the intensity of painful episodes. TNF-α is a rapid-response pro-inflammatory

cytokine that causes muscular catabolism and determines the strength, efficacy, and duration of local and systemic inflammatory reactions [5]. This mediator stimulates the production of soluble TNF receptors (sTNF-R), which act in the regulation of their biological functions [11]. IL-1β production is primarily initiated by TNF-α, which induces IL-6 production. IL-1β is known for its muscle-catabolic properties and has a central role in common with the degenerative processes of aging by acting in the degradation of cartilage in joint inflammation [12].

The presence of LBP in the elderly could, therefore, be another factor that contributes to changes in the regulatory process of inflammation. Wang observed adults with chronic LBP and found that they had elevated TNF-α plasma levels compared to healthy individuals [13]. The evidence indicates that cytokines locally modulate synaptic activity by increasing the efficacy of neural transmission and reducing the nociceptive-response threshold [7]. Cytokine production from local tissue inflammation in LBP exacerbation would therefore be capable of generating/activating pain through this mechanism. Thus, the presence of LBP exacerbation in elderly women is an adverse health condition, it has been shown to lead to an increase in basal inflammatory activity [14].

LBP and increased levels of inflammatory mediators have been linked to functional limitations [15]. A recent study by our research group showed that elderly women with acute LBP presented highest sTNF-R1 plasma levels and the worst performance on mobility tests compared to those without LBP [14].

A prospective study showed an association between pain and sarcopenia in elderly. The results indicated that knee or hip pain predicted loss of muscle strength [16]. However, there are no studies linking sarcopenia and LBP in the elderly.

Considering that the origin of LBP is multifactorial, the inflammatory mediators are recognized as members of the pathophysiology of LBP and sarcopenia, and both are associated with disability, the objective of this study was to compare the intensity and qualities of LBP, plasma cytokine levels (TNF-α, sTNF-R1, IL-1β, and IL-6), and disability in elderly women with acute low back pain who did not have risk for sarcopenia with those at risk for sarcopenia.

MATERIALS AND METHODS

This was a comparative, cross-sectional study approved by the research ethics committee of Federal University of Minas Gerais (ETIC 0100.0.203.000-11). It was formed by a subsample of elderly women with acute low back pain from the Back Complaints in the Elders-Brazil (BACE-Brazil) Study, an international epidemiological study that has been previously published [17]. The participants were divided into two groups: those with and without risk for sarcopenia. Participants were classified according to criteria from the EWGSOP, which has suggested an algorithm for identifying sarcopenia [1].

Sample

The recruitment period was from September 2011 to September 2012. Elderly women from the BACE-Brazil sample were invited, and 155 community-dwelling elderly women provided informed consent according to the procedures of Helsinki. The participants were referred by health care professionals in both public and private primary practice and were recruited by health care centers and peer groups as well as from advertisements in local newspapers, on the radio, and on the Internet.

Inclusion criteria

The inclusion criteria were that the individual had to be a community-dwelling elderly woman at least 65 years old who experienced a new (acute) episode of LBP in which the symptoms had been occurring for fewer than 6 weeks. An episode was considered “new” if the patient had not visited a doctor or other health care provider during the preceding 6 months for the same back complaint [17].

Exclusion criteria

Women with cognitive impairments [18] were excluded. Those with visual, auditory, or motor deficiencies that restricted their ability to complete mobility tests, acute inflammatory disease (C-reactive protein >10 mg/L, verified by tests presented by the participants), neoplasia in the last 5 years, or who were using immunosuppressive drugs were also excluded from the study. It were excluded those with difficulties to walk independently, either by reporting pain or musculoskeletal restriction.

Socio-demographic and clinical characterization

Information on the sample’s characteristics, socio-demographic data, and clinical conditions (e.g., age, education, number of comorbidities, alcohol consumption, smoking status, body mass index) was obtained using a standardized multidimensional questionnaire and physical examinations defined by the BACE research group [17]. The short version of the Geriatric Depression Scale (GDS-15) was used to quantify symptoms of depression [19], and the International Physical Activity Questionnaire (IPAq) was used to investigate the participants’ physical activity levels [20]. Symptoms of depression, physical activity level, and BMI were assessed because they influence inflammatory mediators. The questionnaires were administered by trained researchers.

Sarcopenia

Sarcopenia was assessed according to EWGSOP criteria [1]. Because the relationship between muscle mass and strength was always non-linear, the EWGSOP recommended using both low muscle mass and low muscle function (i.e., strength and performance) to define sarcopenia [1].

The EWGSOP has suggested that sarcopenia screening begin with gait speed measurement (with a <0.8 m/s cut-off point), followed by grip strength (with a 20 kg cut-off point). If gait speed was >0.8 m/s and grip strength was >20 kg, the individual was classified as having risk for sarcopenia. In this case, it should not be indicated the measurement of body composition (muscle mass). Risk for sarcopenia was defined as a gait speed <0.8 m/s, or gait speed >0.8 m/s and grip strength <20 kg. In this case, those who are at risk of sarcopenia should be pointed to measure the muscle mass and sub classified into pre-sarcopenia, sarcopenia or severe sarcopenia [1].
Gait speed was assessed by measuring the duration needed to walk 4.6 m. The participants walked 8.6 m at their typical speed, and the time to complete the test was measured in seconds. The initial and final 2 m were disregarded to account for walking acceleration and deceleration. This test presents good inter- and intra-examiner reliability (0.78 and 0.93, respectively) [21].

Grip strength was measured using a maximal isometric test with the Jamar dynamometer (Sammons Preston, Bolingbrook, IL, USA) for the dominant upper limb. For standardization, the dynamometer was set at the second or third handle position (based on participant preference), and the average of three trials was calculated for a final score; there was a 60-s rest between trials. Participants were positioned according to recommendations by the American Society of Hand Therapy [22].

Plasma levels of inflammatory mediators

To analyze TNF-α, sTNF-R1, IL-1β, and IL-6 plasma levels, 5 mL of blood was drawn from the participants between 8:00 and 10:00 in the morning and immediately centrifuged at 1,500 rpm for 15 minutes to obtain plasma, and stored at −80°C. Plasma levels of sTNF-R1 were assessed with enzyme-linked immunosorbent assays (ELISA) by using a DuoSet ELISA kit (R&D Systems, MN, USA); IL-6 and TNF-α were detected using a high sensitivity kit (Quantikine® HS; R & D Systems), and IL-1 was detected using the Quantikine kit (Quantikine® HS; R & D Systems) according to the manufacturer’s instructions. Readings were taken at 490 nm and transformed into pg/mL. The lower detection limits were 5 pg/mL, 0.15 pg/mL, 0.5 pg/mL, and 3.9 pg/mL for sTNF-R1, IL-6, TNF-α, and IL-1 β, respectively.

Low-back pain characterization

The severity of LBP was assessed with the numerical pain scale, in which “0” indicates no pain and “10” indicates severe pain. This is a simple instrument that is easy to apply and has high reliability and reproducibility [23].

The McGill Pain Questionnaire (MPQ) [24] was used to evaluate the qualities of LBP. It is a multidimensional measure of perceived pain that was designed to measure the sensory, affective, and evaluative aspects of pain. The MPQ is a valid and reliable tool that evaluates both the quality and quantity of pain through use of unique pain descriptors. The score is derived using the Pain Rating Index, which contains 78 pain descriptor items across 20 subclasses and four major subscales. Scores are based on the rank values of the chosen words, higher score indicates worse pain.

Pain frequency was assessed by the standardized question [17], “How often have you had pain in the spine, gluteal region, or legs in the last six weeks?” Frequent pain was defined as responses of “Every day, for at least a few minutes,” “Every day, most of the day,” and “During the entire time.” Infrequent pain was defined as responses of “Less than once a week” and “At least once every week.”

Disability related to back pain

Disability was assessed with the Roland Morris Disability Questionnaire (RMDQ), which has been adapted to and validated for the Brazilian population and offers clinical parameters for the assessment of LBP-related disability. Scores range 0–24 and higher scores indicate increased disability. The questionnaire has high internal consistency (Cronbach’s α = 0.92) and inter-examiner reliability (ICC = 0.95) [25].

Statistical analysis method

Sample characterization was determined using descriptive statistics. The normality of the data distribution was determined using the Kolmogorov-Smirnov test. The Mann-Whitney U was used when the distribution was not normal to verify the differences between inflammatory mediator levels, intensity and quality of pain, and disability across the two groups. The Student’s t-test was used to analyze normally distributed data, which included age, education, and BMI. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS version 17.0; Chicago, IL, USA), with a significance level of 5%.

RESULTS AND DISCUSSION

A description of the clinical and socio-demographic variables is shown in Table (1). The groups were similar on all the socio-demographic variables and clinical conditions analyzed (p > 0.05). The participants were overweight, not suffering from depression, non-smokers, and low alcohol consumers. They had a small number of comorbidities; the most prevalent were hypertension (79.2%), arthritis (50.9%), and diabetes mellitus (32.1%).

There was a significant difference in disability (p = 0.011), LBP severity (p = 0.043), and frequency (p = 0.037) between the two groups (Table 2), indicating that participants at risk for sarcopenia experienced more disability and pain. Participants at risk for sarcopenia had higher sTNF-R1 plasma levels (p = 0.037). There were no significant differences in IL-6 and TNF-α levels between the groups (p > 0.05). IL-1 levels were under the detection limit and were therefore not detected in the sample (Table 3).

Participants at risk for sarcopenia had increased sTNF-R1 levels, increased disability due to LBP, and increased LBP severity and frequency compared to participants without risk for sarcopenia. Although previous studies with young adults found an association between plasma levels of inflammatory mediators and pain, this is the first study to report this relation in elderly patients with LBP.

The association between loss of muscle mass and strength (including the postural muscles) and inflammation may explain the link between sarcopenia and LBP. Inflammatory mediators affect the regulation and transmission of pain stimuli. For example, in pain processes caused by nerve compression, cytokines modulate synaptic activity, thereby increasing the effectiveness of nerve transmission and reducing the threshold for the nociceptive response. [7].

In aging, humans experience chronic subliminal inflammation, with high levels of cytokines, which may result in greater severity and quality of LBP and impact sarcopenia. Inflammatory cytokines have a catabolic effect on muscle [5], which can lead to the loss of strength and muscle function [26]. “Risk for sarcopenia” and “not having sarcopenia”, being evaluated in the present study by gait
Table 1: Socio-demographic and clinical characterization of the elderly women with low back pain.

<table>
<thead>
<tr>
<th></th>
<th>Without risk for sarcopenia (N = 74)</th>
<th>At risk for sarcopenia (N = 81)</th>
<th>p (Mann Whitney U or Student’s t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.76 ± 5.35</td>
<td>71.41 ± 5.55</td>
<td>0.051</td>
</tr>
<tr>
<td>Education (years)</td>
<td>7.47 ± 5.29</td>
<td>7.25 ± 5.29</td>
<td>0.978</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td></td>
<td></td>
<td>0.747</td>
</tr>
<tr>
<td>Married</td>
<td>27</td>
<td>25.9</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>27</td>
<td>32.1</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>9.5</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>36.5</td>
<td>32.1</td>
<td></td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td>0.803</td>
</tr>
<tr>
<td>Never smoked</td>
<td>70.8</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>8.3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>20.8</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption (%)</td>
<td></td>
<td></td>
<td>0.607</td>
</tr>
<tr>
<td>Never</td>
<td>65.3</td>
<td>68.8</td>
<td></td>
</tr>
<tr>
<td>1/month</td>
<td>23.6</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>&gt;2/month</td>
<td>11.2</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>BMI† (kg/m²)</td>
<td>29.47 ± 4.67</td>
<td>30.19 ± 5.51</td>
<td>0.433</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>2.4 ± 1.16</td>
<td>2.46 ± 1.38</td>
<td>0.930</td>
</tr>
<tr>
<td>GDS‡ (0–15)</td>
<td>4.82 ± 3.56</td>
<td>5.28 ± 3.31</td>
<td>0.281</td>
</tr>
<tr>
<td>Physical activity level (MET)</td>
<td>887.84 ± 1,237.65</td>
<td>1,078.52 ± 1,528.37</td>
<td>0.734</td>
</tr>
</tbody>
</table>

Abbreviations: †Body Mass Index; ‡Geriatric Depression Scale.

Table 2: Low back pain and disability in elderly women without and at risk for sarcopenia.

<table>
<thead>
<tr>
<th></th>
<th>Without risk for sarcopenia (N = 74)</th>
<th>At risk for sarcopenia (N = 81)</th>
<th>p (Mann Whitney U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBP Severity</td>
<td>6.34 ± 2.89</td>
<td>7.19 ± 2.80</td>
<td>0.043*</td>
</tr>
<tr>
<td>Pain Rating Index (McGill)</td>
<td>31.9 ± 11.43</td>
<td>33.08 ± 11.14</td>
<td>0.636</td>
</tr>
<tr>
<td>LBP Frequency</td>
<td></td>
<td></td>
<td>0.037*</td>
</tr>
<tr>
<td>Frequent</td>
<td>24.7%</td>
<td>32.4%</td>
<td></td>
</tr>
<tr>
<td>Infrequent</td>
<td>75.3%</td>
<td>67.6%</td>
<td></td>
</tr>
<tr>
<td>Disability (RMDQ 0–24)</td>
<td>12.57 ± 5.60</td>
<td>14.93 ± 5.97</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

Abbreviations: LBP: Low Back Pain; NPS: Numerical Pain Scale; RMDQ: Roll and Morris Disability Questionnaire.

Table 3: Inflammatory mediator plasma levels (pg/mL) in elderly women with acute LBP without or at risk for sarcopenia.

<table>
<thead>
<tr>
<th></th>
<th>Without risk for sarcopenia (N = 74)</th>
<th>Risk for sarcopenia (N = 81)</th>
<th>p (Mann Whitney U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>2.66 ± 3.02</td>
<td>3.28 ± 4.96</td>
<td>0.427</td>
</tr>
<tr>
<td>IL-1β</td>
<td>Not detected</td>
<td>Not detected</td>
<td>-</td>
</tr>
<tr>
<td>sTNF-R1</td>
<td>1,302.9 ± 516.5</td>
<td>1,526.62 ± 728.24</td>
<td>0.035*</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.84 ± 1.71</td>
<td>2.29 ± 2.19</td>
<td>0.137</td>
</tr>
</tbody>
</table>

Abbreviations: TNF α: Tumor Necrosis Factor Alpha; IL-1β: Interleukin; sTNF: Soluble Receptor of TNF-R1; IL: Interleukin-6.

The production and release of inflammatory mediators can occur in response to tissue inflammation, adverse psychosocial conditions, immunosenescence, and the presence of pain [4,6]. The current sample showed no significant differences in psychosocial conditions, lifestyle, or comorbidities between groups, which reinforces the assumption that the increase in the sTNFR-1 may be due to low back pain condition, associated with increased risk of sarcopenia.

Participants at risk for sarcopenia experienced greater pain severity and frequency from LBP than those without risk for sarcopenia. Sarcopenia is a condition that involves speed and grip strength (EWGSOP), confirms the assumption that the loss of strength and function may precede the loss of muscle mass. Based on these results, might infer that inflammatory cytokines could lead to risk for sarcopenia.

TNF-α appears to play a central role in LBP [13], and high levels have been associated with a worse prognosis. For instance, one study followed groups of adults with and without chronic LBP over a six-month period. Higher plasma levels of TNF-α were observed in adults with chronic LBP than those without it on all measurements [13].
neuroendocrine and immune dysregulation. It affects especially type II fibers that are related to power and muscle resistance, and thus can affect the postural balance with consequent loss of normal functioning of the spinal column [27]. Thus, LBP may be associated with sarcopenia. Pain may generate inhibition of efferent stimulation of the motor neurons of the affected muscles [16]. Although there may be atrophy and loss of muscle strength due to LBP, LBP also leads to inhibition of pain-provocative activity, generating a cycle between the loss of strength and pain [16]. Alterations in postural muscles are related to the onset and chronicity of LBP [28].

As expected, our participants at risk for sarcopenia experienced more LBP-related disability than did those without risk for sarcopenia. The evidence shows an association between the intensity and frequency of LBP and disability in functional tasks and activities of daily living [15,29].

The clinical relevance of these results is in the fact that these variables can trigger a cycle, that is, more pain can lead to loss of muscle mass and strength and consequent disability. Similarly, loss of muscle mass and strength can trigger pain and disability. However, to state cause and effect in this study is not possible, and this should be investigated in future studies. At the moment, it is important to note that these relationships may exist and should be investigated in clinical practice.

Studies on the elderly have shown an association between high levels of inflammatory cytokines and reduced functional capacity and muscle function [30]. The process by which cytokines are involved in these alterations has not been fully clarified, but the literature indicates a direct link between high levels of IL-1, IL-6, and TNF-α and the reduction of muscle mass and strength [26]. However, there is evidence that the increase mainly of TNF-α and its receptors play a catabolic effect on muscle protein, which may be related with increased risk of sarcopenia, meaning loss of muscle strength and function and subsequent muscle mass.

A study showed that LBP affected physical capacity and functional performance in a cohort of 956 elderly with different levels of health and functional status. Elderly with LBP were significantly more likely to self-report disability in performing heavy housework, carrying groceries, cutting toenails, and using public transportation than those without LBP [15]. Leveille et al., [29] showed a negative, linear relationship between LBP intensity and gait speed, strength in hip flexion/extension, and performance on the sit-to-stand test.

There are limitations to this study. Because the participants were clinically stable and functionally independent, biochemical analyses (e.g., C-reactive protein, transaminases, urea, lipid parameters, and glucose) were not analyzed. However, future studies should consider these variables. Our study evaluated elderly women with and without risk for sarcopenia, as suggested by EWGSOP, future studies could use body-imaging techniques (i.e., dual-energy X-ray absorptiometry) to estimate muscle mass. However, to consider factors with more predictive power as the loss of global muscle strength seems to be a good strategy for population studies and applicability in primary care. Considering large populations it is believed that the use of the algorithm proposed by EWGSOP help in sorting those to be forwarded later to more complex and higher cost tests. In population cohorts such as the BACE study, self-reporting of health conditions is an accepted methodology because the sample is large and detailed chart review is not feasible. Moreover, the concordance between self-report and medical record review is generally good; nonetheless, the survey is limited because it used self-report to identify LBP. Due to the multidimensional features of LBP, the subjective character of pain, and the potential influence of psycho-emotional, social, and educational variables, the present study considered the importance of a more complete assessment in relation to pain characterization. Future prospective studies should research the progression of LBP, sarcopenia, and other inflammatory mediators associated with pain and immunosenescence.

CONCLUSION

Elderly women at risk for sarcopenia had higher levels of sTNF-R1, greater LBP severity and frequency, and greater disability from LBP than those without risk for sarcopenia.

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