Muscle Mass Gain After Resistance Training Is Inversely Correlated With Trunk Adiposity Gain in Postmenopausal Women

Fábio L. Orsatti,1 Eliana A.P. Nahas,2 Cláudio L. Orsatti,2 Erick P. de Oliveira,3,4 Jorge Nahas-Neto,2 Gustavo R. da Mota,1 and Roberto C. Burini3,4

1Exercise Biology Laboratory (BioEx), Health Science Institute, Triângulo Mineiro Federal University (UFTM), Uberaba, Minas Gerais, Brazil; 2Clinical and Menopause Sector from the Department of Gynecology and Obstetrics, Botucatu School of Medicine, UNESP, Botucatu, São Paulo, Brazil; 3Department of Pathology, Botucatu School of Medicine, UNESP, Botucatu, São Paulo, Brazil; and 4Exercise and Nutrition Metabolism Center from the Department of Public Health, Botucatu School of Medicine, UNESP, Botucatu, São Paulo, Brazil

ABSTRACT

Orsatti, FL, Nahas, EAP, Orsatti, CL, de Oliveira, EP, Nahas-Neto, J, da Mota, GR, and Burini, RC. Muscle mass gain after resistance training (RT) and associate these changes with the hypertrophy of muscle mass (MM) in postmenopausal women (PW). The investigation used a sample that consisted of 22 PW (44–69 years old). The group was subjected to RT (60–80% of 1 repetition maximum) for the total body 3 d wk–1. Body composition (dual-energy x-ray absorptiometry) and plasma hormone, E2 (immunolite system), and interleukin-6 (IL-6; enzyme-linked immunosorbent assay) were assessed at the beginning and end of the experiment. After RT, only women who acquired up to 5% TA gained MM, whereas women who acquired >5% TA exhibited increased IL-6 and no MM gain (p < 0.05). The ΔMM was negatively associated with time of menopause (r = −0.45, p < 0.05) and positively associated with baseline IGF-1 (r = 0.47, p < 0.05). Only ΔLE (leg extension) was negatively associated with baseline IL-6 (p < 0.05). Trunk adiposity growth (ΔTF, kilograms) was positively correlated with changes in IL-6 (r = 0.68, p < 0.05). The MM gain was negatively correlated with ΔTF (r = −0.63, p < 0.05) and changes in IL-6 (r = −0.73, p < 0.05). After adjusting all of the confounding variables, only baseline IGF-1 (positively) and changes in IL-6 (negatively) influenced MM, and only the increase in TA influenced IL-6. Our study suggests that increased levels of TA during RT increase IL-6 concentrations, which is a significant negative predictor of MM gain in PW.

KEY WORDS strength exercise, hypertrophy, abdominal fat

INTRODUCTION

A loss of strength and muscle mass (MM) is an independent predictor of mortality in the elderly and patients with chronic disease (31). Additionally, muscle function is an important determinant of functional capacity among elderly women and has been associated with an increased risk of falls, increased mobility disability, and osteoporotic fractures (31,36).

High serum levels of inflammation markers, such as interleukin-6 (IL-6) and C-reactive protein, are strong predictors of disability, independent of other known risk factors (4,14,32). Specifically, previous studies suggested that sarcopenia is associated with increased concentrations of circulating IL-6 (26,33), particularly in older women (12,25). Possibly because of the transition to postmenopause, sex hormones decrease to very low levels, leading to a remodeling of body mass, reflected in adipose tissue redistribution and MM loss (28,37). Because adipocytes from visceral adipose tissue release 2- to 3-fold more IL-6 than those from subcutaneous depots do, even small increases in visceral fat during menopause might have a large impact on circulating IL-6 levels. Moreover, evidence suggests that decreases in ovarian function per se may lead to increases in IL-6 and other proinflammatory cytokines (17,28). This conclusion is supported by the preventive effect of hormonal therapy (27,28,37). Thus, a proinflammatory state may be one of the key factors in decreased strength and MM among postmenopausal women (PW) with abdominal obesity.

Although previous studies have suggested that IL-6 is associated with sarcopenia, the mechanism by which chronic inflammation affects MM and physical function has not been
fully established. Evidence suggests that elevated levels of IL-6 per se may negatively affect muscles (5,15). Haddad et al. reported that chronic local infusion of nonsystemic doses of IL-6 into targeted skeletal muscles in adult rats led to significant muscle atrophy (15). Additionally, IL-6 can activate adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscle cells and suppress protein synthesis in rats by downregulating mammalian target of rapamycin (mTOR) signaling (3,6). Alternatively, van Hall et al. reported that acute systemic infusion of IL-6 into healthy human subjects at the same levels as those reported during intense exercise reduced the availability of plasma amino acids in muscle (40).

Furthermore, evidence indicates that increased IL-6 levels can affect strength and MM by interfering with the intracellular signaling route of anabolic hormone transduction (growth hormone [GH] and insulin-like growth factor-1 [IGF-1]) (15) and reducing the synthesis or control of the biological activity of growth factors (e.g., IGF binding protein [IGFBP]) (11). This suggests a biological link between IGF-1 and IL-6 (47). In contrast to the findings of the studies described above, IL-6 has the potential to stimulate myoblast or satellite cell proliferation, both of which characterize hypertrophy (34). However, studies have verified that chronic IL-6 exposure can have catabolic effects on skeletal muscles (5,15,16,30), suggesting that the paradoxical effects of IL-6 exposure may be related to temporal factors.

The IGF-1 is a metabolic and anabolic growth factor that promotes protein accretion and muscle hypertrophy (21). Moreover, some authors postulated that circulating IGF-1 is a biomarker for assessing changes in body composition (19–21). An epidemiological study performed in older women found that low plasma IGF-1 levels were associated with poor knee extensor muscle strength, slow walking speed, and self-reported difficulty with mobility tasks. This suggests a role for IGF-1 in disability in the elderly (8). When examining the combined effects of low IGF-1 levels and high IL-6 levels, women with IGF-1 levels in the lowest quartile and IL-6 levels in the highest quartile had a significantly greater limitation in walking and disability in mobility tasks and instrumental daily activities (adjusted odds ratios, 10.77, 5.14, and 3.66) and a greater risk for death (adjusted relative risk, 2.10) compared with those with high IGF-1 levels and low IL-6 levels. Thus, the combination of low IGF-1 levels and high IL-6 levels confers a high risk for progressive disability and death in older women (9). The authors suggested a potential effect of IL-6 and IGF-1 in the regulation of the homeostatic mechanisms that maintain adequate MM. For example, IL-6-mediated decreases in IGF-1 production may be a potential mechanism by which chronic inflammation mediated by abdominal obesity causes MM and physical function impairment in PW. Increased abdominal fat increases IL-6 concentrations, and this is a significant negative predictor of MM (33) gain in PW.

Resistance training (RT) effectively restores MM and strength in PW (24). Mechanical loading leads to the activation of mechanical tension sensors that possess the ability to translate tension into chemical signals that interact with gene and protein signaling networks, allowing cytoskeletal proteins to replace and renew themselves (1). Other factors, such as endocrine responses to resistance exercise (testosterone, GH, IGF-1, insulin, and cortisol) also contribute to hypertrophy (1,24). We recently reported that changes in circulating IGF-1 were positively correlated with MM gain in PW (45–70 years old) who underwent 16 weeks of RT (24). Nevertheless, the slower repair and adaptation of skeletal muscle in elderly people may result from chronic inflammation (23,26). Resistance training–induced reductions in inflammatory makers were recently found to be associated with hypertrophy in elderly women (23). Increased abdominal fat during postmenopausal weight-bearing exercise affects RT-induced hypertrophy, indicating the importance of abdominal fat assessment during RT.

The aim of this study was to evaluate the effects of trunk adiposity (TA) on hypertrophy after 9 months of RT in PW. We also evaluated whether any of the parameters studied could be used as predictors of MM changes during RT. We hypothesized that increased TA increases IL-6 concentrations, which, in turn, affects the development of muscle hypertrophy in PW after RT.

**Methods**

**Experimental Approach to the Problem**

This study was conducted to evaluate the effect of abdominal fat on MM and strength in PW. Based on the 50th percentile of change for the amount of TA after 9 months of RT, the women were separated into 2 groups: women who gained up to 5% TA (≤5%) and women who gained >5% TA (>5%). Pretest and posttest measurements were then performed. We then evaluated whether any of the studied parameters could be used as predictors of MM changes during RT.

**Subjects**

The population group consisted of women who had been followed at the university’s Climacterium Hospital, Menopause Outpatient Unit, and School of Medicine’s Nutrition and Exercise Metabolism Center. Sedentary women whose amenorrhea had occurred at least 12 months previously and whose follicle-stimulating hormone (FSH) values were >40 mIU·ml⁻¹ were included in the study. Diabetic women with uncontrolled hypertension, with untreated thyroid disease, who had been using statins; who underwent hormone therapy up to 6 months before the beginning of the study; or who had cancer, rheumatoid arthritis, joint diseases, or disabling muscle diseases, were excluded. Eighty-three menopausal women were selected to participate in the study. Many women who had refused to participate in the project reported that they did not have the time necessary for exercise. The main reasons were that they had to work or perform household chores. Thus, only 39 menopausal women aged 40–70 years agreed to perform physical training. Moreover, during the 9 months of intervention, 17
women withdrew themselves from the study because of illness or family problems or they thought that participating in the study was troublesome. Each participant was required to sign a university Institutional Review Board-approved informed consent form regarding the risks and requirements of the study before participation.

**Anthropometric Evaluation**

A platform-type anthropometric scale (Filizola, Brazil), graded every 100 g, with a capacity up to 150- and 0.1-kg precision, was used to measure weight. The subjects were barefoot and wore minimal clothing when they were weighed. Height was determined using a wall-mounted portable stadiometer (Seca, Brazil) with a precision of 0.1 cm. The criteria recommended by the World Health Organization were applied to determine the body mass index (BMI = weight/height²).

The subjects’ waists were measured at the medium point between the last rib and iliac crest using an inexensible cellulose measuring tape divided into centimeters (total length = 1.5 m). The patients were measured in an orthostatic position, and a waist circumference ≤ 88 was considered normal.

**Body Composition Assessment**

Total-body dual-energy x-ray absorptiometry was performed using a Hologic QDR-2000 densitometer plus scanner (Hologic, Waltham, MA, USA). This was manually used to directly measure body fat. To minimize interobserver variations, all scans and analyses were performed by the same evaluator, and the day-to-day percent coefficient of variation was <1.0% for the total body. The total-body scan was divided into arms, legs, trunk, and head. Body composition was analyzed using 5.73A for total body.

**Laboratory Analysis**

To minimize diurnal variations, all the blood samples were obtained in the morning between 7:00 AM and 9:00 AM after an overnight fast. The blood samples were collected by venous puncture in a vacuum-sealed system (Vacutainer, BD Diagnostics, Franklin Lakes, NJ, USA). Twelve milliliters of blood was collected directly into a dry tube that held the gel to separate the serum that was then divided into 2 samples. To prevent hemolysis, the plates were centrifuged for 10 minutes (3,000 rotations per minute), and 1 sample was immediately analyzed to assess biochemical parameters. Serum from the second sample was stored at −80°C until hormones and IL-6 levels could be read at once in a single assay.

Follicle-stimulating hormone, luteinizing hormone (LH), estradiol (E₂), and IGF-1 were measured. The hormones were quantified using the IMMULITE System (Siemens Healthcare Diagnostics, Deerfield, IL, USA), which uses solid-phase immunoassays obtained by chemiluminescence that are used in an automatic analyzer to quantitatively determine hormone levels. In such a system, all the steps are performed automatically, and the standard curve, which is predesigned and stored in the equipment, is used to estimate the sample’s results. The sensitivities for total IGF-I, FSH, LH, and E₂ were 20 μg·dl⁻¹, 0.1 mIU·ml⁻¹, 0.1 mIU·ml⁻¹, and 15 pg·ml⁻¹, respectively. Intraassay variances for total IGF-I, FSH, LH, and E₂ were 3.1–4.3, 2.6–3.7, 4.8–6.5, and 6.3–15%, respectively.

Plasma IL-6 levels were measured using the enzyme-linked immunosorbent assay immunoenzymatic method (Quantikine High Sensitivity Human, R&D Systems, Minneapolis, MN, USA) according to the manufacturer’s protocol. The minimum detectable concentration (0.039 pg·ml⁻¹), within-assay precision (6.9–7.8%), and interassay precision (6.5–9.6%) were determined by the manufacturer. These values were tested 20 times in 3 known samples.

**Maximum Strength Assessment**

The maximum strength assessment was supervised by a qualified professional and conducted at the same time each day for all women (at 4:00 PM). At baseline, all the women were verbally informed about a healthy diet and were suggested to maintain their regular diet during the test days and training period.

In the maximum strength assessment test, the maximum load that an individual could bear during a given exercise, involving muscle groups either using free weights or muscle-building machines, was quantified. Before the test, the participants performed 3 exercise sessions on alternate days to familiarize themselves with the equipment and techniques for each exercise. In this test, a subjective load was determined for the warm-up, and then 5–10 repetitions with loads of 40–60%
of the 1 repetition maximum (1RM) were performed. After the warm-up, the participants were allowed to rest for 1 minute, and the musculature involved in the exercise relaxed. Afterward, 3–5 repetitions were performed that ranged from 60 to 80% of 1RM. The weight was then increased considerably, and the individuals attempted to perform the movement. If a subject was unable to perform the movement, then they had 3–5 minutes of rest before the next attempt with a new load. Attempts proceeded until a load equivalent to 1RM was found for each exercise. The load adopted as the maximum weight was the weight of the last exercise successfully performed in a complete movement by the individual. During the test, the individuals were advised to avoid respiratory apnea.

### Resistance Training Protocol

The weight training was supervised by a qualified professional and was conducted for 9 months (March to November) at least 2 d wk−1 in a gymnasium for women. No exercise other than RT was allowed. Before the beginning of the protocol, the participants were subjected to a 4-week learning period to adapt themselves to the protocol. During that period, the exercises were performed with lighter loads and fewer series, beginning with a 15-repetition series with loads between 40 and 50% of the maximum. The progression was gradual and maintained a series of 8–12 maximum repetitions with 60–80% of the maximum weight. During the training period, every 3 months, the load was adjusted to keep it in the training zone (8–12 maximum repetitions).

The protocol consisted of dynamic exercises for the upper and lower limbs for a total of 50 minutes. For the larger muscle groups (e.g., chest, back, and thighs), 2 exercises per muscle group were performed. For the smaller muscle groups (e.g., biceps and triceps), one exercise was performed. The training protocol was the following: thighs (leg press, leg extension [LE], and leg curl), chest

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**Table 2.** Body composition, interleukin-6, and muscle strength for postmenopausal women at baseline and 9 months, separated into 2 groups: women who gained ≤5% of trunk adiposity (≤5%) and those who gained >5%.*

<table>
<thead>
<tr>
<th></th>
<th>≤5% (n = 11)</th>
<th>&gt;5% (n = 11)</th>
<th>P: group</th>
<th>P: time</th>
<th>P: group × time</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM (kg)</td>
<td></td>
<td></td>
<td>0.403</td>
<td>0.752</td>
<td>0.049</td>
</tr>
<tr>
<td>Before</td>
<td>31.9 ± 5.5</td>
<td>34.5 ± 4.9</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>After</td>
<td>32.8 ± 5.4</td>
<td>33.9 ± 4.4</td>
<td>0.327</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TA (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>12.9 ± 3.8</td>
<td>13.2 ± 3.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>12.8 ± 3.9</td>
<td>15.5 ± 3.5†</td>
<td>0.395</td>
<td>0.080</td>
<td>0.013</td>
</tr>
<tr>
<td>IL-6 (pg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Before</td>
<td>1.5 ± 1.1</td>
<td>1.6 ± 0.8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>After</td>
<td>1.4 ± 0.9</td>
<td>2.2 ± 1.2†</td>
<td>0.722</td>
<td>0.014</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Of fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>41.7 ± 5.3</td>
<td>40.8 ± 4.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>41.1 ± 5.6</td>
<td>43.5 ± 5.1†</td>
<td>0.319</td>
<td>&lt;0.001</td>
<td>0.868</td>
</tr>
<tr>
<td>LE (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>32.5 ± 9.9</td>
<td>28.3 ± 7.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>41.8 ± 9.3</td>
<td>37.2 ± 6.8</td>
<td>0.601</td>
<td>&lt;0.001</td>
<td>0.577</td>
</tr>
<tr>
<td>PD (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>34.3 ± 4.5</td>
<td>33.3 ± 7.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>52.7 ± 7.5</td>
<td>50.0 ± 11.4</td>
<td>0.830</td>
<td>&lt;0.001</td>
<td>0.576</td>
</tr>
<tr>
<td>SR (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>30.5 ± 9.3</td>
<td>30.4 ± 6.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>47.1 ± 9.8</td>
<td>48.9 ± 7.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MM = muscle mass; IL-6 = interleukin-6; TA = trunk fat; LE = leg extension; PD = pack deck; SR = seated row.
†p < 0.05.

**Table 3.** Correlation between Δ for MM and ΔMM and strength (ΔLE, ΔPD, and ΔSR) vs. other variables at baseline (n = 22).*

<table>
<thead>
<tr>
<th>Values at the baseline</th>
<th>MM</th>
<th>ΔMM</th>
<th>ΔLE</th>
<th>ΔPD</th>
<th>ΔSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>−0.26</td>
<td>−0.27</td>
<td>−0.01</td>
<td>0.38</td>
<td>0.29</td>
</tr>
<tr>
<td>TM (y)</td>
<td>0.04</td>
<td>−0.45†</td>
<td>0.10</td>
<td>0.39</td>
<td>0.22</td>
</tr>
<tr>
<td>IL-6 (pg ml⁻¹)</td>
<td>0.25</td>
<td>0.09</td>
<td>−0.46†</td>
<td>0.04</td>
<td>−0.16</td>
</tr>
<tr>
<td>FSH (mIU ml⁻¹)</td>
<td>0.33</td>
<td>0.19</td>
<td>0.17</td>
<td>0.01</td>
<td>−0.10</td>
</tr>
<tr>
<td>LH (mIU ml⁻¹)</td>
<td>0.13</td>
<td>−0.16</td>
<td>0.27</td>
<td>−0.26</td>
<td>0.12</td>
</tr>
<tr>
<td>E2 (pg ml⁻¹)</td>
<td>0.45†</td>
<td>−0.26</td>
<td>−0.29</td>
<td>0.16</td>
<td>0.27</td>
</tr>
<tr>
<td>IGF-1 (ng dl⁻¹)</td>
<td>0.08</td>
<td>0.47†</td>
<td>−0.20</td>
<td>−0.31</td>
<td>−0.05</td>
</tr>
</tbody>
</table>

*MM = muscle mass; IL-6 = interleukin-6; TA = trunk fat; LE = leg extension; PD = pack deck; SR = seated row; TM = time of menopause; FSH = follicle-stimulating hormone; LH = luteinizing hormone; E₂ = estradiol; IGF-1 = insulin growth factor; Δ = the difference between the final and baseline.
†p < 0.05.
(bench press and peck deck), back (seated row and lat pull-down), triceps (tricep pulley), biceps (bicep curl).

All the loads were individually measured for each exercise after the 1RM test. These loads were periodically adjusted according to the complementary gain of weight and to best adapt the training. This way, exercise intensity was kept to the same. During the protocol, abdominal exercises (3 series of 30 repetitions) and calf muscle exercises (3 series of 20 repetitions with body weight) were also performed.

Breathing was controlled by exhaling during the concentric action and inhaling during the eccentric action of the exercise to prevent apnea. A period of 90–120 seconds of rest was established between the series and exercises. During the training sessions, the participants were advised to perform eccentric actions in 1 second and concentric actions in 1 second.

Statistical Analyses
The data distribution was determined using the Kolmogorov-Smirnov test. Means and maximum and minimum values were used to characterize the sample. According to the 50th percentile of change for the amount of TA, the women were separated into 2 groups: women who gained up to 5% TA (≤5%) and women who gained >5% TA (>5%). To compare values before and after RT, we used repeated-measures analysis of variance (ANOVA). To determine the relationships between variables, the following analyses were used: correlation coefficient, partial correlation coefficient (controlled for confounding factors), and multiple regression analysis forward stepwise regression (to determine which variables contributed more to the criterion prediction).

Changes in MM over time (final minus initial) and IL-6 were both used as dependent variables. Age, IL-6, TA, MM, GC, and IGF-1 at baseline, time of amenorrhea, assiduity (2 or 3 times per week), and changes (final minus initial) in TA, GC, MM, IL-6, and IGF-1 were the independent variables. Differences between baseline and posttreatment values were analyzed using the paired t-test. Predictors that showed a promising prognostic value (p < 0.05) based on the ANOVA were further analyzed using correlation coefficient and regression analyses, receiver-operator characteristic (ROC) curve analysis, and sensitivity, specificity, and likelihood-ratio tests. The positive likelihood ratio (PLR) was calculated as sensitivity/(1 – specificity), indicating the degree to which the posttest probability of achieving MM gain increases given a positive result in the baseline test. Similarly, the negative likelihood ratio was calculated as (1 – sensitivity)/specificity, indicating the degree to which the posttest probability of achieving MM gain decreases given a negative result in the baseline test. The significance level was set at 5%.

Results
Clinical, hormonal, and inflammatory characteristics as body composition indicators in women subjected to RT are shown in Table 1. Of the menopausal women, 68% were classified as overweight or obese, 96% had high body fat, and 82% had high
abdominal fat with normal MM (Table 1). The IGF-1 values were classified as normal (normality defined as 55–225 ng ml\(^{-1}\) for IGF-1). Only one woman had values above the normality range (322 ng ml\(^{-1}\)). The IL-6 values (1.46–4.05 pg ml\(^{-1}\)) were classified as normal (Table 1).

Table 2 shows the values for body composition, IL-6, and MM from the PW baseline and after 9 months. The women were separated into 2 groups: women who acquired <5% TA (<5%) and women who acquired >5% TA (>5%). After RT, only the women who acquired <5% TA gained MM (\(p < 0.05\)). However, when the women were combined (\(n = 22\)), the values were not significantly different. Only the women who acquired >5% TA exhibited increased IL-6, TA, and percent fat. Both groups had improved muscle strength in each of the exercises. Both groups had similarly increased muscle strength (Table 2).

Muscle mass at baseline and strength changes after the intervention (\(\Delta = M_1 - M_0\)) were correlated with age, time of menopause (TM), FSH, LH, E\(_2\), IL-6, and IGF-1 (Table 3). Baseline MM was positively and significantly associated with E\(_2\), whereas \(\Delta\)MM (MM change) was negatively and significantly associated with TM and positively with baseline IGF-1 (Figure 1). Only \(\Delta\)LE was negatively and significantly associated with baseline IL-6.

Table 4 and Figures 2 and 3 show that \(\Delta\)MM and \(\Delta\) muscle strength were correlated with \(\Delta\)FSH, \(\Delta\)LH, \(\Delta\)E\(_2\), \(\Delta\)IL-6, \(\Delta\)IGF-1, and \(\Delta\)TA. The \(\Delta\)MM was significantly associated with \(\Delta\)TA and \(\Delta\)IL-6, and \(\Delta\)SE was significantly associated with \(\Delta\)IL-6.

Similarly, \(\Delta\)IL-6 was correlated with assiduity, AG, TM, TA, \(\Delta\)TA, GC, \(\Delta\)GC, IGF-1, \(\Delta\)IGF-1, and IL-6. Significance was found only with \(\Delta\)TA (\(r = 0.69, p < 0.001;\) Figure 4).

To identify the best predictors for MM changes (\(\Delta\)), a multiple regression analysis was conducted (Table 5). The forward stepwise regression analysis showed that \(\Delta\)IL-6, initial IGF-1, initial FSH, E\(_2\), TM, and initial E\(_2\) were the determining variables for \(\Delta\)MM, explaining 76% (\(R^2\)) of the change. However, only \(\Delta\)IL-6 and IGF-1 were significant (\(R^2 = 67\%\)). Additionally,
the effect of initial IGF-1 was potentiated when controlled by the other variables (partial correlation, Table 5).

Similarly, to identify the best predictors for muscle strength change (Δ), a multiple regression analysis was conducted (Table 6). The forward stepwise regression analysis showed that ΔIL-6 and IL-6 were the determining variables for Δ muscle strength, explaining 20, 40, and 40% ($R^2$) of LE, PD, and SR, respectively.

The forward stepwise regression analysis showed that ΔTA and ΔGC were the determining variables for ΔIL-6, explaining 53% ($R^2$) of the change. However, only ΔTA was significant. Additionally, the effect of ΔTA was potentiated when controlled by ΔGC ($r = 0.72$, $p < 0.001$).

For the ROC analysis, 11 volunteers (50%) achieved MM gain. Of all of the measures, only baseline IGF-1 (area under the curve [AUC] = 0.769, 95% confidence interval [CI] = 0.542–0.919, $p = 0.012$), ΔIL-6 (AUC = 0.825, 95% CI = 0.607–0.956, $p < 0.001$), and ΔTA (AUC = 0.851, 95% CI = 0.636–0.965, $p < 0.001$) had a significant ROC curve. The ROC analysis suggested threshold scores of >98.2, ≤–0.096, and ≤932.7 for IGF-1, ΔIL-6, and ΔTA, respectively, at baseline as predictors of individuals who gained MM. This analysis indicated that the subjects with a baseline value greater than the ROC-derived threshold score of >98.2 would have a posttest probability of 68.7% (PLR = 2.2, 95% CI = 1.3–3.8) of having increased MM over baseline. Similarly, the subjects with a baseline value ≤98.2 would have a posttest probability of 0.0%. Values less than or equal to the ROC-derived threshold scores of ≤–0.096 and 932.7 for ΔIL-6 and

![Figure 4. Correlation between Δs (the difference between the final and baseline) for trunk fat and interleukin-6 (IL-6) after 9 months of resistance training in postmenopausal women ($r = 0.67$, $p < 0.05$).](image-url)

**Table 5.** Multiple regression analysis and partial correlation of variables and its association with ΔMM after 9 months of resistance training in postmenopausal women ($n = 22$).*

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>Partial correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔIL-6 (pg·mL$^{-1}$)†</td>
<td>−0.60</td>
<td>−0.75</td>
</tr>
<tr>
<td>Initial IGF-1 (ng·dl$^{-1}$)†</td>
<td>0.35</td>
<td>0.57</td>
</tr>
<tr>
<td>Initial FSH (mIU·dl$^{-1}$)</td>
<td>0.20</td>
<td>0.35</td>
</tr>
<tr>
<td>ΔE$_2$ (pg·dl$^{-1}$)</td>
<td>0.32</td>
<td>0.23</td>
</tr>
<tr>
<td>TM (y)</td>
<td>−0.19</td>
<td>−0.19</td>
</tr>
<tr>
<td>Initial E$_2$, (pg·dl$^{-1}$)</td>
<td>0.16</td>
<td>0.12</td>
</tr>
</tbody>
</table>

IL-6 = Interleukin-6; FSH = follicle-stimulating hormone; LH = luteinizing hormone; E$_2$ = estradiol; IGF-1 = insulin growth factor; TM = time of menopause.

†$p < 0.05$.  

**Table 6.** Multiple regression analysis and partial correlation of variables and its association with ΔLE, ΔPD, and ΔSR after 9 months of resistance training in postmenopausal women ($n = 22$).*

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>Partial correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔLE</td>
<td>0.20†</td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg·mL$^{-1}$)</td>
<td>−0.49†</td>
<td></td>
</tr>
<tr>
<td>ΔPD</td>
<td>0.40†</td>
<td></td>
</tr>
<tr>
<td>TM (y)</td>
<td>0.49†</td>
<td>0.53</td>
</tr>
<tr>
<td>ΔIL-6 (pg·mL$^{-1}$)</td>
<td>−0.46†</td>
<td>−0.51</td>
</tr>
<tr>
<td>ΔSR</td>
<td>0.40†</td>
<td></td>
</tr>
<tr>
<td>ΔIL-6 (pg·mL$^{-1}$)</td>
<td>−0.57†</td>
<td>−0.60</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.35</td>
<td>0.40</td>
</tr>
</tbody>
</table>

†$p < 0.05$.  

* Indicates significance at $p < 0.05$.  

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ΔTA would have posttest probabilities of 100 and 78.6% (PLR = 3.7, 95% CI = 2.6–5.3), respectively, of gaining MM over baseline. The subjects with a baseline value \( \pm 0.096 \) and 932.7 would have posttest probabilities of 31.3 and 0% for ΔIL-6 and ΔTA, respectively.

**Discussion**

This study evaluated the effects of TA on the development of MM and whether any of the parameters studied could predict MM changes in PW who underwent 9 months of RT. The main findings were that the changes in TA had a strong negative association with changes in MM and strength. Muscle change was positively associated with total baseline IGF-1 levels and negatively associated with ΔIL-6. The latter, in turn, was positively correlated with TA gain but not with total-body fat gain. Muscle strength change was negatively associated with ΔIL-6 and IL-6 concentrations. We conclude that the changes in MM during long periods of RT in PW are directly related to total IGF-1 and inversely related to TA and IL-6, with correlations between the last 2. Our data also support the use of IGF-1 and IL-6 as biomarkers to track changes in body composition (19,20).

We observed a strong association between TA and ΔIL-6 (Figure 2). Only PW who had gained >5% TA had increased IL-6 (Table 2). Additionally, the regression analysis showed that TA and GC changes represented 53% of ΔIL-6. However, only TA showed significance. Consistent with this assumption, other studies showed that plasma levels of IL-6 are positively correlated with TA in healthy elderly men and elderly patients with type-2 diabetes (27,33). Furthermore, plasma levels of IL-6 were correlated with BMI only in PW, and such a relationship was lost in women with hormone replacement (38). Women tend to accumulate visceral fat during menopause, which is possibly involved in estrogen-dependent mechanisms of energy expenditure and fat redistribution and can be reversed by hormone replacement (28). Adipose tissue can be a significant source of increased proinflammatory cytokine production in PW (15). Interleukin-6 can increase estrogen synthesis in adipose tissue by stimulating aromatase activity and thus the conversion of C19 androgenic steroids to estrogens (41).

Because adipose tissue is a major source of estrogen biosynthesis in PW, this can work as a negative feedback mechanism to limit increases in IL-6 (28).

This study showed that changes in the concentrations of IL-6 were related to changes in abdominal fat, influencing both the development of MM and strength during RT in PW. Only the women who had gained >5% TA showed no hypertrophy and increased IL-6. Women who gained no TA showed no increase in IL-6 and hypertrophy after 9 months of RT (Table 2). Furthermore, these results were confirmed by the strong correlation among ΔMM, ΔIL-6, and ΔTA. The regression analysis showed that ΔIL-6 was the main determinant of ΔMM (Tables 4 and 5). The role of IL-6 in the development of disability and mortality in older people has been widely documented (4,12,14,25,32,33). Ogawa et al. showed that training-induced changes in muscle thickness were associated with a reduction in inflammatory markers (tumor necrosis factor-α and C-reactive protein) (23). Muscle loss and a high risk of disability were suggested to be associated with high levels of IL-6 in serum, which could be explained by the catabolic effect of IL-6 on muscles, resulting in early sarcopenia (3,5,15,16,40). Recently, van Hall et al. (40) infused IL-6 (rhIL-6) into healthy individuals and found a substantial reduction in plasma amino acids with a concomitant reduction of 50% in muscle protein turnover but with a slight increase in lipolysis attributable to a larger decrease in catabolism-related synthesis. The authors hypothesized that the substantial reduction observed in muscle protein turnover and slight increase in lipolysis were primarily caused by a reduction in available amino acids and not directly mediated by IL-6. When administering subcutaneous rhIL-6 into rats for 7 days, Janssen et al. (16) concluded that the cause of peripheral muscle atrophy was the redistribution of cardiac flow that resulted from myocardial failure induced by IL-6. Some authors have shown that, in the absence of systemic effects, IL-6 directly induces skeletal muscle atrophy in healthy rats (15). Additionally, IL-6 also shows disproportional effects on the myofibrillar protein compartment and is associated with decreased synthesis of muscle proteins (15). Interleukin-6 can activate AMPK in skeletal muscle cells and suppress protein synthesis in the rat by downregulating mTOR signaling (3,6). Furthermore, IL-6 can interact with the JAK/STAT signaling pathway, leading to changes in suppressors of cytokine signaling (SOCS) expression. This process may in turn lead to reduced signaling associated with GH or IGF-1 receptors (2,15). Additionally, IL-6 can be associated with the activation of E3-ubiquitin-protein ligase (MAFbx/Atrogin), leading to muscle protein degradation (5).

This study also showed that total baseline IGF-1 had a moderate association with MM changes (22%, partial correlation; Table 3). Interestingly, when baseline IGF-1 was corrected with IL-6 changes, the association increased to 33% (partial correlation), identifying a possible interaction between factors (Table 5). Circulating concentrations of IGF-1 increase with RT in PW (24,35,39), but this finding has not been universal (7,10). Of the 5 studies mentioned above, 4 used 12–21 weeks of training, and 3 reported increased concentrations of IGF-1, and this change in IGF-1 was positively associated with respective changes in MM (10,24,35,39). Only Borst et al. used a training period similar to that of our study, and they found no increase in the total IGF-1 (7). However, unlike Borst et al., we found that total baseline IGF-1 was associated with a hypertrophic response (33% association). The IGF-1 plays an important role in the regulation of somatic growth, metabolism and survival, and cellular differentiation and proliferation (21). Although circulating concentrations of IGF-1 are regulated by nutrition, insulin, and GH, evidence indicates that physical
exercise is another important regulator of IGF-1 concentrations (21). Increased work load, by removing synergist muscles, induces the expression of IGF-1 in muscle, thus stimulating hypertrophy by mechanisms that are independent of circulating GH. Additionally, this excludes the systemic effect of IGF-1 because only the exercised muscle hypertrophied (2). Despite this, Nindl et al. recently found that the circulating bioavailability of IGF-I had a moderate association with physical activity–induced increases in MM accretion in young, healthy women, and this association was greater than the association observed for total IGF-1 (20). Additionally, some studies in older individuals showed a positive association between circulating levels of IGF-1 and muscle strength, MM, walking speed, and mobility (21,24,35).

The IGF-1 and ΔIL-6 concentrations were the main predictive variables for ΔMM, and they were potentiated when they were controlled in between each other (Table 5). These findings suggest that increased IL-6 levels can regulate IGF-1, inasmuch as its effects are lost. In contrast, the effects of IGF-I on muscles are detected when IL-6 concentrations are low. The combined effects of IL-6 and IGF-1 have been associated with muscle strength and power in older individuals, MM in sarcopenic obese people, and limitations in walking, disability in mobility tasks, disability in the instrumental activities of daily living, and mortality in older women (4,9). However, such an effect on RT-dependent MM gain in PW has not been previously investigated. Our study provides evidence of a multifaceted relationship between plasma concentrations of IL-6 and IGF-1 in the development of RT-induced MM. IL-6 inhibits IGF-1 synthesis, and IL-6 blocks the effects of IGF-1 (22). Previous studies have suggested that proinflammatory cytokines often act as negative regulatory signals that temper the action of hormones and growth factors. Additionally, IL-6 can interfere with the GH-IGF-1 axis by diminishing IGF-1 synthesis and controlling its biological activity by stimulating the hepatic expression of IGFFBP-4 (21,22).

The studies cited above and our present results suggest that IGF-I, ΔIL-6, and ΔTA are mediators of RT-induced hypertrophy or may be biomarkers of poor health without any pathogenic effects of their own. If IGF-1, ΔIL-6, and ΔTA are indeed mediators, then interventions that raise IGF-1 and lower ΔIL-6 and ΔTA may have beneficial effects on MM and strength in PW who undergo RT. Even if IGF-1, ΔIL-6, and ΔTA are not directly in the causal pathway that leads to RT-induced hypertrophy, they still have potential clinical utility in the assessment of changes in MM and strength in PW who undergo RT.

**Practical Applications**

Our results suggest that IGF-1, ΔIL-6, and ΔTA are mediators of RT-induced hypertrophy or may be biomarkers of poor health without any pathogenic effects of their own. If IGF-1, ΔIL-6, and ΔTA are indeed mediators, then interventions that raise IGF-1 and lower ΔIL-6 and ΔTA may have beneficial effects on MM and strength in PW who undergo RT. Even if IGF-1, ΔIL-6, and ΔTA are not directly in the causal pathway that leads to RT-induced hypertrophy, they still have potential clinical utility in the assessment of changes in MM and strength in PW who undergo RT.

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