Effects of Megestrol Acetate on Circulating Interleukin-15 and Interleukin-18 Concentrations in Healthy Elderly Men

Charles P. Lambert,1 Michael G. Flynn,2 Dennis H. Sullivan,1 and William J. Evans1

1Nutrition, Metabolism, and Exercise Laboratory, Donald W. Reynolds Center on Aging, University of Arkansas for Medical Sciences, and Geriatric Research, Education and Clinical Center, Central Arkansas Veterans Healthcare System, Little Rock.
2Wastl Human Performance Laboratory, Department of Health, Kinesiology, and Leisure Studies, Purdue University, West Lafayette, Indiana.

Background. Interleukin-15 (IL-15) and interleukin-18 (IL-18) are potential regulators of body composition in humans. The authors previously reported that megestrol acetate ingestion causes a large accumulation of adipose tissue and reduces muscle mass. Therefore, the purpose of this investigation was to evaluate the effects of megestrol acetate ingestion on circulating IL-15 and IL-18 concentrations in healthy elderly men.

Methods. All participants received 800 mg of megestrol acetate per day during this 12-week study. Megestrol acetate was combined with testosterone injections (100mg/week), placebo injections, resistance training, or resistance training and testosterone. Resting IL-15 and IL-18 concentrations were measured by enzyme-linked immunosorbent assay at week 0 (pre), week 6 (mid), and week 12 (post).

Results. The time effect for IL-15 was significant (p = .0008), with the mid and post values being significantly greater than the pre value. The change in IL-15 concentration was not significantly related to the change in muscle mass (r = -.31; p > .05), nor was it related to the change in fat mass (r = .17; p > .05). Differences among groups or over time were not significant for IL-18, nor were correlations between pre body weight and pre IL-18 (r = -.03), pre fat mass and pre IL-18 (r = .14), or the change in fat mass and the change in IL-18 (r = -.07).

Conclusions. IL-15 was increased as a result of megestrol acetate ingestion; however, megestrol acetate did not affect circulating IL-18 concentrations, and the change in IL-18 did not correlate with any body composition variables.
Resistance training.—Groups receiving MA and resistance training (RT+P) and MA, testosterone, and resistance training (RT+T) used Keiser resistance training machines (Keiser Sports Health Equipment, Fresno, CA), as previously described (9).

Testosterone administration.—Testosterone (testosterone enanthate; 100 mg/week) was delivered via intramuscular injection in a double-blind, placebo-controlled manner to groups T and RT+T.

Measurements
Measurements were made before the interventions (pre), after 6 weeks (mid), and after 12 weeks (post).

Table 1. Descriptive Characteristics for Study Participants

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (y)</th>
<th>Height (m)</th>
<th>Body Mass (kg)</th>
<th>BMI (kg/m²)</th>
<th>% Body Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (N = 6)</td>
<td>64.0 ± 5.3</td>
<td>1.77 ± 0.07</td>
<td>66.5 ± 9.4</td>
<td>21.2 ± 2.9</td>
<td>20.2 ± 11.9</td>
</tr>
<tr>
<td>RT + P (N = 5)</td>
<td>67.0 ± 6.1</td>
<td>1.77 ± 0.08</td>
<td>70.6 ± 12.2</td>
<td>22.5 ± 2.8</td>
<td>22.0 ± 10.3</td>
</tr>
<tr>
<td>T (N = 6)</td>
<td>66.6 ± 3.7</td>
<td>1.76 ± 0.05</td>
<td>75.2 ± 8.1</td>
<td>24.3 ± 1.8</td>
<td>26.6 ± 2.2</td>
</tr>
<tr>
<td>RT + T (N = 8)</td>
<td>66.9 ± 5.5</td>
<td>1.74 ± 0.07</td>
<td>69.8 ± 11.2</td>
<td>22.9 ± 2.9</td>
<td>19.1 ± 2.9</td>
</tr>
</tbody>
</table>

Note: BMI = body mass index; P = placebo; RT = resistance training; T = testosterone.

Whole-Body Plethysmography
Body density was determined by air displacement plethysmography (Life Measurement Instruments, Concord, CA). Fat mass and fat-free mass were calculated using the formula of Siri (17): % body fat = 4.950/Db – 4.50 [Db, body density]. These results have been reported previously (9).

Computed Tomography
Computed tomographic scans of the dominant thigh were obtained at its greatest circumference using a GE Scanner (GE, Milwaukee, WI) operating at 120 kV, 200 mA, with a scanning time of 1 second, as previously reported (9).

Cytokine Measurements
Venous blood was sampled at 7:00 AM after the participant had been in the supine position for 15 minutes.

Figure 1. Plasma interleukin-15 (IL-15) (picograms per milliliter) concentrations before the interventions (pre), after 6 weeks of the interventions (mid), and after 12 weeks of the interventions (post). Values are the mean ± standard error. RT+T = resistance training and testosterone; RT+P = resistance training and placebo; T = testosterone; P = placebo.
Plasma IL-15 and serum IL-18 levels were measured by enzyme-linked immunosorbent assay (R&D systems, Minneapolis, MN). Standard curves were calculated using DataFit 8.0 (Oakdale Engineering, Oakdale, PA). All values are reported as the mean ± standard error.

**Statistical Analyses**

Three-factor analysis of variance (hormone status × resistance training status × time) with repeated measures on time was used, followed by Tukey post hoc analysis. Data were significant at an alpha level of .05 or less.

**RESULTS**

A significant time effect was observed for IL-15 (p = .0008), with the mid and post time points being greater than the pre point (Figure 1). The change in IL-15 was not significantly related to the change in muscle mass (r = -.31; p > .05), nor was it related to the change in fat mass (r = .17; p > 0.05). No significant differences were observed for IL-18 (Table 2). Furthermore, no significant correlations were observed between IL-18 and pre body weight (r = -.03), IL-18 and pre fat mass (r = .14), or the change in IL-18 and the change in fat mass (r = -.07). Table 3 lists the previously reported (9) changes in body weight, muscle mass, and fat mass.

**DISCUSSION**

The major finding of this investigation was that IL-15 was significantly increased as a result of MA ingestion. Increases were 28.6% and 29.7% for the mid and post time points, respectively. Similarly, Okada and colleagues (18) reported that progesterone administration increased IL-15 production in vitro in human endometrial stromal cells. Megestrol acetate, and more generally progesterone, appears to have a regulatory effect on systemic cytokine concentrations. We previously reported that MA reduces circulating IL-6 and a regulatory effect on systemic cytokine concentrations. We have shown that progesterone administration reduces IL-6 (20–22) and TNF-α (23) production in various cell lines. Along with the increase in IL-15, the changes in IL-6 and TNF-α would be assumed beneficial because IL-6 and TNF-α are implicated in muscle wasting (24), whereas elevated IL-15 is anabolic to muscle and catabolic to fat (14).

However, it is clear from our investigation that muscle mass decreased substantially with MA ingestion and fat mass increased considerably (Table 3). The changes in circulating cytokine concentrations with MA apparently were insufficient to influence changes in muscle mass. Different or more potent mechanisms may be responsible for the decrease in muscle mass at the tissue level. Also unknown is the magnitude and the duration of changes in systemic cytokines required for changes in muscle mass. However, reducing inflammatory cytokine concentrations appears to induce weight gain in certain disease states.

Reyes-Teran and coworkers (25) administered thalidomide (which decreases TNF-α production) to persons with the acquired immunodeficiency syndrome and reported weight gain and lessening of disease severity. Because we did not find the expected relationship between systemic cytokines and body composition in this investigation, the effects of short-term modest changes in circulating cytokines on the sarcopenia of normal aging may be of questionable importance. Chronic elevations in circulating cytokines likely influence muscle mass in elderly persons (26).

Previous research found that IL-18 is elevated in obese women compared with those of normal weight and that circulating IL-18 levels decrease with weight loss (15). Furthermore, IL-18 was shown to be significantly correlated with body weight and visceral fat mass (15). We could not show an increase in IL-18 with a 3.8 kg gain in body weight and a 4.7 kg gain in fat mass in men. In addition, we found no significant relationship between preintervention body weight and IL-18 or between preintervention fat mass and IL-18. The lack of relationship between IL-18 and body composition, as reported previously (15), might be explained by the fact that we studied men rather than women. Perhaps IL-18 is a more important regulator of body composition in men than in women. Circulating testosterone plays an important role in the regulation of body composition in men (27).

**Conclusion**

The ingestion of MA increased IL-15 concentrations, whereas IL-18 concentrations were unaltered. The change in circulating IL-15 level was not significantly related to changes in muscle mass or fat mass and therefore may be of limited clinical importance in elderly persons.

**ACKNOWLEDGMENTS**

The authors thank the employees of the General Clinical Research Center, Arlene Sullivan, advanced practice nurse, and Scott Freeling for their technical assistance with this project.

Supported by a grant from Bristol-Myers Squibb, by National Institutes of Health grants M01-RR-12488 (General Clinical Research Center), RO1-AG-15385 (to W.J.E.), and F32-AG-05873 (to C.P.L.).

Address correspondence to Charles P. Lambert, PhD, Nutrition, Metabolism, and Exercise Laboratory, Donald W. Reynolds Center on Aging, University of Arkansas for Medical Sciences, Little Rock, AR 72205. E-mail: lambertcharlesp@uams.edu
REFERENCES


Accepted April 25, 2003