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

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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.

MEGESTROL acetate (MA) is a synthetic progestin used to stimulate weight gain in cancer, the acquired immunodeficiency syndrome, and geriatric cachexia (1–8). Previously we reported that MA ingestion substantially increases fat mass and reduces muscle mass in elderly men (9). Progesterone administration increases adipocyte cell size (10), which may be due in part to its stimulatory effect on lipoprotein lipase activity (11). Progesterone also increases the activity of fatty acid synthase, which catalyzes the synthesis of long-chain fatty acids from malonyl coenzyme A (12). Furthermore, progesterone-treated rats have reduced brown adipocyte oxygen consumption (13).

Interleukin-15 (IL-15) and interleukin-18 (IL-18) are potent cytokines that appear to play a role in regulating body composition (14,15). IL-15 administration reduces white adipose tissue mass by 33% in rats (15), apparently as a result of its direct action on adipocytes (16). Circulating IL-18 levels were greater in obese women than in normal-weight women, and weight loss reduced circulating levels of IL-18 (15). Because of the role these two cytokines play in regulating adipose tissue mass, and because MA substantially increases adipose tissue mass in humans, we studied the effects of MA on circulating levels of IL-15 and IL-18.

METHODS

Participants

The Human Research Advisory Committee at the University of Arkansas for Medical Sciences approved this study. All participants gave written consent before the study began. Elderly men (aged 60 to 85 years) with a body mass index $\geq$ 25 kg/m² were invited to participate (Table 1). They were medically stable, generally healthy, and had stable weights for the previous 2 months. Reasons for exclusion were metastatic disease, exertional angina, and any condition that prevented resistance training.

Study Design

All participants received MA. Group P received a placebo injection (saline) for 12 weeks, group RT+P received weekly placebo injections and resistance training, group T received testosterone, and group RT+T received testosterone and resistance training.

Interventions

Megestrol acetate ingestion.—Participants in all groups ingested 800 mg/day MA each day during the entire study.
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).

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 = 4.95/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.

### 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.

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 were 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 \( (r = .17; p > .05) \). 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 tumor necrosis factor-\( \alpha \) (TNF-\( \alpha \)) (19). Other investigators have shown that progesterone administration reduces IL-6 (20–22) and TNF-\( \alpha \) (23) production in various cell lines. Along with the increase in IL-15, the changes in IL-6 and TNF-\( \alpha \) would be assumed beneficial because IL-6 and TNF-\( \alpha \) 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-\( \alpha \) 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 the 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.

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