Megestrol Acetate-Induced Weight Gain Does Not Negatively Affect Blood Lipids in Elderly Men: Effects of Resistance Training and Testosterone Replacement

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Megaestrol acetate (MA), a synthetic 17-alpha-hydroxyprogesterone derivative, is used to stimulate appetite and induce weight gain in individuals with cancer and AIDS (1-6) and in overweight elderly men and women (7,8). The majority of the weight gain with MA has been shown to be adipose tissue (1,2). Therefore, we combined testosterone replacement and/or resistance training with MA ingestion in an attempt to partition more of the weight gain toward skeletal muscle tissue and to reduce the accrual of adipose tissue (9). MA alone induced a reduction in skeletal muscle mass, which was attenuated by resistance exercise training but not by testosterone replacement. Resistance training and testosterone administration while on MA induced a significant increase in muscle mass. Furthermore, testosterone administration with MA ingestion reduced adipose tissue accrual compared to that observed when testosterone was not administered. Because of the considerable increase in appetite, energy intake, and adipose tissue accrual when MA was ingested, there was the potential for adverse changes in blood lipids. In addition, resistance training and/or testosterone replacement may have altered blood lipids.

The purpose of this investigation was to evaluate the effects of MA ingestion alone and in combination with testosterone replacement and/or resistance training on circulating total cholesterol (TC), high density lipoprotein (HDL) cholesterol, triglycerides, and the TC to HDL ratio (TC/HDL).

Methods

Experimental Subjects

This study was approved by the Human Research Advisory Committee at the University of Arkansas for Medical Sciences. All subjects gave written consent prior to their participation. Men with a body mass index of ≤25 kg/m² who were between the ages of 60 and 85 years were recruited for the study. Subjects were medically stable, generally healthy (all medical problems were under control and medication dosage was stable), and had been weight stable for the previous 2 months. After completing a preliminary medical history form and signing consent forms, subjects had the following tests performed: (a) a 12-lead electrocardiogram; (b) a screening blood draw to assess routine clinical measures; and (c) a health history and physical. Subjects were excluded for the following reasons: metastatic cancer, exertional angina, or any condition that prevented resistance training. The descriptive characteristics for these subjects are provided in Table 1.

Study Design

MA has consistently been shown to stimulate appetite and weight gain. The purpose of this study was to evaluate the effects of MA, with testosterone and/or resistance training (RT), on circulating lipid concentrations. This was a randomized, double-blind (with respect to testosterone or placebo administration), controlled trial. Four groups were
studied in this investigation. All subjects received MA. Group P received a placebo injection (saline) for 12 weeks (n = 7); group RT+P received weekly placebo injections and RT for 12 weeks (n = 6); group T received testosterone replacement for 12 weeks (n = 8); and group RT + T received testosterone replacement and resistance training for 12 weeks (n = 7).

Interventions

MA ingestion.—Oral daily ingestion of MA (800 mg/day) was initiated at the beginning of the study and continued for the duration of the study. Subjects were asked to ingest the MA with breakfast.

Resistance training.—For the groups receiving MA and resistance training (RT + P) and MA, testosterone, and resistance training (RT + T), Keiser pneumatic resistance training machines (Keiser Sports Health Equipment, Fresno, CA) were used for whole-body progressive resistance training, as previously described (9).

Testosterone administration.—Testosterone was administered in a double-blind placebo-controlled fashion. For groups that received testosterone (T) and testosterone and resistance training (RT + T), a once weekly intramuscular injection of testosterone enanthate (100 mg) was administered starting on the first day of training, and the injection was repeated on the same day of the week for 11 more weeks. For groups P and RT + P, the same volume of isotonic saline was injected once weekly.

Measurements

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

Blood lipid measures.—Venous blood was sampled from an antecubital vein at 7:00 AM after subjects awoke. All blood samples were obtained after the subject had been in the supine position for at least 15 minutes. Blood samples were obtained Thursday morning after a Wednesday morning injection of testosterone for the mid time point and Thursday morning 8 days after the final injection for the post time point. Total cholesterol was measured using the method originally described by Stadman (10) and adapted for use by Flegg (11), Roschlauf and colleagues (12), and Rautela and Liedtke (13). HDL cholesterol was determined

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Figure 1. Serum total cholesterol (mg/dl). A significant time effect was observed, with the mid and post time points being significantly lower than the pre time point. Mean in the legend (and the fifth bar at each time point) refers to the average of all four groups.

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using the AHDL Cholesterol assay system (Dade Behring, Newark, DE). Serum triglycerides were measured using the enzymatic bichromatic methods of Hagen and Hagen (14) and Rautela and colleagues (15).

Statistical Analyses
Three-factor analysis of variance (hormone status × resistance training status × time) with repeated measures on time (pre, mid, post) was used. When a significant effect was observed, the Tukey post hoc analysis was applied. Data were considered significant at or below an alpha level of ≤0.05.

RESULTS
A significant time effect was observed for total cholesterol (p = 0.0006; Figure 1), with the mid and post time points being significantly lower than the pre time point. No other significant differences were observed. Similarly, a significant time effect (p = 0.0003; Figure 2) was observed for HDL cholesterol, with the mid and post time points being significantly lower than the pre time point. No other significant differences were observed for HDL cholesterol. For TC/HDL, no significant differences between groups or over time (time effect; p = 0.24) were observed (Table 2). For triglycerides, there tended to be a time effect (p = 0.061), with the mid and post time points being lower than the pre time point; however, this difference did not reach statistical significance (Table 2).

DISCUSSION
The major finding of this study was that despite a 3.8-kg increase in body weight over 12 weeks with MA (all groups combined), the great majority of which was adipose tissue, there was no significant change in the TC/HDL, a very good indicator of coronary heart disease risk (16). The results from this study indicate that a worsening of the blood lipid profile, as measured by the TC/HDL, does not appear to be a concern if MA-induced weight gain is to be undertaken in otherwise healthy underweight elderly men. To our knowledge, this is the first study to investigate blood lipid changes resulting from MA ingestion in elderly men.

In women, Guven and colleagues (17) reported a 13.5% decline in total cholesterol over 3 months at a dose of 160 mg of MA/day, while Farish and colleagues (18) reported a 15.4% drop in total cholesterol in women ingesting 40 mg/day of MA. In the present investigation we found a 5.6% drop in total cholesterol in men taking 800 mg of MA across study groups. Thus, it appears that the magnitude of decline in total cholesterol is greater in women than in men despite the much larger dosage of MA administered in the present

<table>
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<tr>
<th>Table 2. Total Cholesterol to High-Density Lipoprotein (HDL) Cholesterol Ratio (TC/HDL) and Triglyceride Concentrations (TAG; mg/dl). No Significant Differences (p &gt; .05) for Either Parameter</th>
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Note: RT = group receiving resistance training; T = group receiving testosterone; P = group receiving placebo.
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investigation. The reduction in HDL with MA in this investigation (−12.2%) is similar to that observed by Guven and colleagues (17) (−11.9%) but less than that observed by Farish and colleagues (18) (−20.3%), both of whom studied women. As indicated by the significant time effect, the decrease in total and HDL cholesterol was an effect of MA above and beyond the effects of resistance training and/or testosterone replacement.

Under conditions in which MA is not ingested, testosterone administration in elderly men results in a drop in HDL cholesterol and no change in total cholesterol, thus increasing the total cholesterol to HDL cholesterol ratio (19,20). It appears that although HDL cholesterol was reduced with MA ingestion, the reduction in total cholesterol with MA was great enough to prevent an increase in the TC/HDL associated with testosterone replacement.

Resistance training in the elderly increased HDL cholesterol and decreased the TC/HDL ratio (21,22). From our finding of a reduction in HDL cholesterol regardless of group, it would appear that 800 mg/day of MA had a greater effect in decreasing HDL cholesterol than resistance training had an effect in increasing HDL cholesterol in this investigation.

MA is often used in AIDS patients in an attempt to increase body weight (1,3,5). In addition, the use of protease inhibitors is widespread in individuals with AIDS. A side effect of protease inhibitor administration in AIDS patients is substantial increase in total cholesterol and triglycerides (23,24). Although the present study did not evaluate the effects of MA on blood lipids in AIDS patients, further research is warranted on MA and blood lipids in this patient population.

In conclusion, MA is a potent stimulator of appetite and weight gain in underweight elderly individuals; however, when it is administered alone, the majority of the weight gain is adipose tissue, and there is a loss of muscle mass. For individuals who ingest MA, more beneficial changes in muscle mass and adipose tissue mass will be seen if resistance training, alone or in combination with testosterone replacement, is undertaken. Based on our data, it appears that MA does not cause adverse blood lipid changes, and, therefore, the decision to use MA should be based on other factors.

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