The Correlation of Cytokine Levels With Body Weight After Megestrol Acetate Treatment in Geriatric Patients

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Background. Cachexia is associated with elevated levels of cytokines in cancer and human immunodeficiency virus patients. Studies in cancer and acquired immunodeficiency syndrome patients showed that treatment with megestrol acetate (MA) is associated with improvement in appetite and weight gain. Reduction in the levels of cytokines is associated with weight gain in laboratory animals with cancer. This study evaluates the correlation between changes in cytokine (or their receptor) levels and weight following MA treatment in geriatric weight-loss patients.

Methods. Veterans Administration Medical Center nursing home patients (N = 69) with a weight loss of ≥5% of usual body weight over the past 3 months or body weight 20% below their ideal body weight participated in a 12-week, randomized, double-blind, placebo-controlled trial, with an additional 13-week follow-up period. Patients were randomly assigned to receive a placebo or MA oral suspension of 800 mg/d for 12 weeks. Levels of the following cytokines (or their receptors) were measured at baseline and after 12 weeks of treatment: tumor necrosis factor soluble receptor (TNFR) subunits, TNFR-p55 and TNFR-p75; interleukin 6 (IL-6); and the soluble interleukin-2 receptor (sIL-2R). The subjects’ weight and body composition were measured at the start of the study. Weight and mortality were followed up for another 13 weeks after discontinuing the MA study drug.

Results. Elevated levels of IL-6 in almost all geriatric cachexic patients, compared with normal volunteers (mean, <4.6 pg/ml), were noted at baseline. At 12 weeks after the study drug treatment, there was a decrease in cytokine levels (or their receptors) in the MA group (mean change in IL-6, −3.63 ± 6.62 pg/ml; TNFR-p55, −0.06 ± 0.11 ng/ml; TNFR-p75, −0.01 ± 0.29 ng/ml; and sIL-2R, 0.08 ± 0.07 ng/ml) and the placebo group (mean change in IL-6, −2.08 ± 3.92 pg/ml; TNFR-p55, −0.02 ± 0.08 ng/ml; TNFR-p75, −0.20 ± 0.18 ng/ml; and sIL-2R, 0.02 ± 0.03 ng/ml). Although the change in cytokine levels was not statistically significant between the two groups, significant negative correlation (p < .05) was found. For example, increased weight correlated with decreased sIL-2R levels (r = −.36) and TNFR-p75 (r = −.31); fat-free mass (FFM) gain and reduction of sIL-2R (r = −.39), TNFR-p75 (r = −.30). There was a significant correlation between weight gain and reduction of TNFR-p75 (r = −.54), TNFR-p55 (r = −.47), and sIL-2R (r = −.53); FFM gain and reduction of sIL-2R (r = −.59), TNFR-p75 (r = −.41), TNFR-p55 (r = −.42); and fat gain and reduction of TNFR-p75 (r = −.41) in the MA group (p < .05), but not in the placebo group.

Conclusions. Although there was no significant change in cytokine levels between the two groups, the reduction in cytokine levels after MA treatment correlated with improvement in weight, fat mass, and FFM at 12 weeks.

Weight loss among elderly patients is a common clinical problem. Wasting and cachexia (1–3) are associated with severe physiological, psychological, and immunological consequences, regardless of the underlying causes. In the geriatric population, anorexia and cachexia leading to diminished host defenses are often unexplained (4). Although it is obvious that reduced oral food intake due to anorexia or gastrointestinal obstruction plays an important role in the development of cachexia, progressive weight loss is also a prominent feature of both neoplastic disorders and chronic infections. Anorexia is a common clinical manifestation of many disease states (5). Investigators hypothesize that chronic production of certain cytokines can explain the nonspecific responses, which result in cachexia in cancer (6), acquired immunodeficiency syndrome (AIDS), and rheumatoid arthritis patients (7). Production of cytokines, such as tumor necrosis factor (TNF), interleukin 6 (IL-6), and interleukin 2 (IL-2), may be involved in geriatric cachexia and/or anorexia as well.

Cytokines rarely act alone. They stimulate a variety of cell types to produce and secrete a cascade of other cytokines (8). Cytokines may inhibit feeding by causing not only nausea and vomiting but also by decreasing gastric motility and emptying (intestinal motility) or by modifying gastric acid secretion (9,10). The effects of cytokines may result from direct effects on the gastrointestinal system.
Cytokine Levels After MA Treatment

METHODS

Study Approval and Subjects

The Northport Veterans Administration Medical Center (VAMC) Institutional Review Board approved this study. Legal guardians signed consent forms for mentally incompetent patients. A baseline Karnofsky status was performed. Patients were randomized to treatment with 20 ml of a placebo or an oral suspension (800 mg) (MEGACE; Bristol-Myers Squibb, Princeton, NJ) every morning at 10 am (2 hours after breakfast) for 12 weeks.

Inclusion Criteria

To qualify for study participation, male and female patients must have resided at the Northport VAMC nursing home; been ≥55 years old at the time of the study; experienced weight loss ≥5% of their usual body weight during the previous 3 months or had a body weight 20% below their ideal weight (based on the tables of the Metropolitan Life Insurance Company and the Gerontology Research Center or, for patients aged older than 69 years, based on the Veterans Administration/National Institute on Aging’s geriatric assessment tables for height and weight); had a life expectancy of ≥24 weeks; and had a Karnofsky performance status of ≥40%.

Exclusion Criteria

Patients were excluded from the study if they had any of the following conditions: poorly controlled hypertension or congestive heart failure; evidence of dehydration, ascites, or mechanical obstruction of the alimentary tract; untreated systemic infections or other serious intercurrent illnesses; received steroids, androgens, or other progestational agents; or experienced weight loss due to hyperthyroidism or depression.

Randomization

Patients were randomized to treatment on an individual basis by means of a random number table.

Blinding

Patients and staff (with the exception of the statistician responsible for randomization and the pharmacist who dispensed the study drug) were blinded to study treatment throughout the active treatment phase and the 3-month follow-up period.

Study Treatment and Evaluations

The study drug and placebo were supplied in identical containers with nonidentifying labels. The baseline evaluation included a medical history, physical examination, complete blood counts, and laboratory chemistry and body composition tests (by bioelectrical impedance analysis [BIA] using standard tetrapolar methods; model BIA-101Q with fluid/nutrition software, version 3.1b, RJL Systems, Clinton Township, MI) (26). Weight and body compositions were determined at 4-week intervals. We used the same scale (marked with scale number) each time a patient was weighed, and standardized the scale each time. If the change of weight was more than 4 lbs, the patient was reweighed twice within the next 2 days until the difference of the three consecutive weights was less than 1 lb.

Cytokine Assays

One tube of serum was collected from the participants (between 12 and 1 pm) at baseline and at Week 12. The serum was immediately frozen at −70°C. For all cytokine assays, samples were thawed at room temperature. We chose to assay the soluble TNF-α receptors, TNFR-p75 and TNFR-p55, because TNF production itself is episodic, the plasma half-life is too short, and random sampling is too imprecise. Increased levels of the receptor subunits are indirect measures of local TNF-α response. Measurement of IL-6 (Biosource International, Camarillo, CA), the TNF-p55 receptor, the TNFR-p75 receptor, and the soluble IL-2 (sIL-2) receptor (Roche Diagnostics, Basel, Switzerland) was performed using enzyme immunoassay kits (according to the manufacturer’s instructions) run on the Roche Cobas Core II (Roche Diagnostics, Basel, Switzerland). These test kits are bead-based, solid-phase, sandwich-enzyme immunoassay methods. The normal range of 141 apparently healthy blood donors in the Cobas Core for TNF-p55 was 0.4 to 1.7 ng/ml; for TNFR-p75, 2.0 to 5.5 ng/ml; for sIL-2R, 0.04 to 0.95 ng/ml (mean ± 2 SD); and for IL-6, <4.17 pg/ml. Three to five patients did not have enough volumes to run all the cytokine tests (sIL-2R missed three samples, TNFR-
p55 missed four samples, and IL-6 and TNFR-p75 missed five samples). One other MA-treated patient was noted to have significantly higher cytokine levels than the other patients for unknown reasons. Data from this patient were treated as outliers and excluded from the analyses. Samples were analyzed in duplicate, and variation was found to be <5%. The reproducibility was as follows: The intra-assay and inter-assay coefficients of variation were <7.5% over the whole measuring range.

Statistical Analysis

Efficacy analyses were performed on patients who completed the 12-week study and were without major protocol violations. Analyses in this report included only patients who had cytokine assays performed. The relationship between the changes in cytokine levels and weight were evaluated by the partial correlation using multivariate analysis of variance, adjusting for the treatment factor in the overall study group. Pearson correlation coefficients were also calculated in separate study groups. For variables, such as cytokine levels, between group comparison was performed using the t test and the analysis of covariance (ANCOVA), adjusting for baseline values. Descriptive statistics were expressed as mean ± standard error. The Statistical Analysis System (SAS Institute, Cary, NC) was used to perform these analyses (27). All statistical tests were two sided. Significant levels were considered at p < .05.

RESULTS

Patient Characteristics

Sixty-nine patients were randomly assigned to receive a placebo (n = 33) or MA (n = 36). Of the 69 patients, 51 completed the 12-week trial. There were no differences in the baseline characteristics of those who completed the trial and those who withdrew (Figure 1). At baseline, no statistically significant differences were noted between the two groups with respect to age (mean age, 76.60 ± 4.1 vs 76.5 ± 1.2 years old), gender (25 men and 1 woman vs 23 men and 2 women), Karnofsky performance status (55.5 ± 1.4 vs 52.1 ± 1.6 cerebral vascular accident), or prestudy weight loss (11.3% ± 1.5% vs 11.4% ± 1.5%) in the MA and placebo groups, respectively. There was no difference in the baseline medical diagnosis and history (including infections) between both groups (p = .5). The most common diagnoses included the following: cardiovascular diseases (22 vs 24 subjects); cerebral vascular accident (13 vs 9 subjects); chronic obstructive pulmonary disease (9 vs 9 subjects); dementia (13 vs 15 subjects); hip fractures (13 vs 8 subjects); diabetes mellitus (9 vs 6 subjects); and depression (17 vs 13 subjects) in the MA and placebo groups, respectively. During the 12-week treatment period, there was no difference in overall medication usage or intercurrent medical problems between the two groups (p = .70). There were no differences in infections during the trial (seven vs eight events) in the MA and placebo groups, respectively, nor in the history of infections immediately prior to the enrollment in the study. No difference in infections in the 3-month follow-up period or in overall mortality up to a year following the study was noted between the two groups.

Weight

As seen in Table 1, baseline body weight measurements were similar in the MA (61.26 ± 1.8 kg) and the placebo (61.46 ± 2.54 kg) groups. After 12 weeks of treatment, although the difference was not statistically significant, the mean weight change in the MA group (1.36 ± 0.99 kg) was greater than that of the placebo group (0.94 ± 0.76 kg). After including three additional patients who completed the 12-week active trial phase and had data on weight, but not cytokine measurements, no statistical significant difference in mean weight change was found between the placebo (0.91 ± 0.68 kg; n = 25) and MA groups (1.05 ± 1.0 kg; n = 26). The results of an intent-to-treat analysis (ITT; consisting of all 68 patients [33 placebo, 35 MA] who received at least one dose of study medication and one weight determination in addition to the baseline) also showed no statistical significant difference in weight change between the two groups (placebo, 0.45 ± 0.64 kg; MA, 0.50 ± 0.86 kg). By Week 20, a statistically significant (p = .037) difference in mean weight gain existed. The MA group gained 2.45 ± 1.1 kg, whereas the placebo group lost 0.41 ± 0.82 kg. By Week 25, the MA-treated group had a mean weight gain of 2.95 ± 1.41 kg, and placebo patients had a mean weight loss of 0.45 ± 0.86 kg (p = .043). Of the 7 placebo patients who gained more than 4 lbs during the first 12 weeks of the study, only 3 were able to maintain their new weight. The greater percentage of MA-treated patients with a weight gain of ≥1.82 kg was significant (p = .011) compared with placebo-treated patients. Differences were also seen in the ANCOVA of weight, after adjusting for baseline weight, which was statistically significant at Week 20 (p = .039) and almost reached significance at Week 25 (p = .055).

Body Composition (BIA)

No differences in baseline body composition between the two groups were observed, as determined by BIA. Although the changes in body composition between the two treatment
groups did not achieve statistical significance at 12 weeks, the increase in total fat tended to be higher in the MA-treatment group (1.42 ± 0.62 kg) compared with that of the placebo group (0.32 ± 0.68 kg; \( p > .20 \); Table 2).

### Cytokine Levels and Their Relationship to Weight and Body Composition

There was no statistically significant difference in cytokine levels between the two groups at baseline, except for a higher level of TNF-p55 in the MA patients, which made its reduction following MA treatment more significant. Significant levels of IL-6 (normal, \(<4.17\) pg/ml) were detected in patients with weight loss at the baseline (Table 1). The placebo group started with lower cytokine levels. At Week 12, similar to the findings in weight gain, decreased levels of cytokines (or their receptors) were noted, although there was no significant difference in levels of cytokine values between the MA and the placebo groups, using the ANCOVA, after adjusting for baseline value (Table 2). Additional analyses of cytokine levels using log transformation also did not show significant difference between the two groups.

As noted previously, there were equal numbers of infections in the MA and placebo groups, both leading up to the study period and during the active treatment period. In a subgroup analysis, there was no statistically significant difference if patients who had infections were left out of the analysis between the two groups, in terms of the changes in cytokine levels and FFM (\( p > .20 \); Table 3). Patients who did not gain weight (or reduce their cytokine levels) were those who had infections during the trial (\( p = .01 \)). The weight changes in the MA (\( n = 20 \)) and the placebo (\( n = 19 \)) groups for those patients without infections were 2.56 ± 1.05 kg versus 0.42 ± 0.74 kg (\( p = .13 \)). The fat changes in the MA (\( n = 20 \)) and the placebo (\( n = 18 \)) groups of those patients without infections were 1.76 ± 0.66 kg versus \(-0.28 ± 0.63\) kg (\( p = .04 \); Table 3). The results of ITT analysis, which included 29 patients in the placebo group and 30 patients in the MA group who underwent cytokine measurements, also did not show statistical differences between groups, except for sIL-2R (placebo, \(-0.02 ± 0.03\) ng/ml vs MA, \(0.10 ± 0.06\) ng/ml), where borderline significance was noted (ANCOVA, \( p = .08 \)).

Although no significant differences were found in the weight gain and reductions in the levels of cytokines between the MA and the placebo groups at Week 12, changes in cytokine levels were negatively correlated with the changes in weight (\( p < .05 \)); increased weight correlated with decreased sIL-2R (\( r = -.36 \)) and TNF-p75 (\( r = -.31 \)). Changes in the FFM were negatively correlated with sIL-2R (\( r = -.39 \)) and TNF-p75 (\( r = -.30 \)). On the other hand, there was no statistically significant correlation between fat mass and cytokine changes (\( p > .20 \); Table 4).

When stratifying by study groups, no significant correlation between cytokine level reduction and weight gain, or fat gain and FFM gain, was found in the placebo group. However, there was a significant correlation between weight gain and reduction of TNF-p55 (\( r = -.47 \)), TNF-p75 (\( r = -.54 \)), and sIL-2R (\( r = -.53 \)); between FFM gain and reduction of sIL-2R (\( r = -.59 \)), TNF-p75 (\( r = -.41 \)), and

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### Table 1. Baseline Cytokine Levels, Weight, Fat, and FFM in Placebo and MA-Treatment Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>MA Treatment</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>n</td>
<td>Mean ± SE</td>
<td>Range</td>
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<tr>
<td>IL-6 (pg/ml)</td>
<td>24 26.03 ± 4.7</td>
<td>3.01–76.43</td>
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<tr>
<td>TNF-p55 (ng/ml)</td>
<td>25 1.80 ± 0.19</td>
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<tr>
<td>TNF-p75 (ng/ml)</td>
<td>25 5.51 ± 0.45</td>
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<tr>
<td>sIL-2R (ng/ml)</td>
<td>25 0.55 ± 0.07</td>
<td>0.13–1.59</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>25 52.19 ± 1.33</td>
<td>40.91–67.36</td>
</tr>
<tr>
<td>Fat (kg)</td>
<td>25 9.12 ± 0.77</td>
<td>4.0–17.86</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25 61.26 ± 1.8</td>
<td>45.91–80.55</td>
</tr>
<tr>
<td>n</td>
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<td>Range</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>22 17.42 ± 3.4</td>
<td>0.74–62.06</td>
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<tr>
<td>TNF-p55 (ng/ml)</td>
<td>23 1.34 ± 0.12</td>
<td>0.62–2.39</td>
</tr>
<tr>
<td>TNF-p75 (ng/ml)</td>
<td>22 4.36 ± 0.38</td>
<td>2.40–8.10</td>
</tr>
<tr>
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<tr>
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<td>22 9.3 ± 1.09</td>
<td>1.77–21.64</td>
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<tr>
<td>Weight (kg)</td>
<td>23 61.46 ± 2.54</td>
<td>31.36–85.09</td>
</tr>
</tbody>
</table>

Notes: Normal range of cytokines (taken from 141 apparently healthy blood donors in Cobas Core II); MA = megestrol acetate; FFM = fat-free mass. IL-6, \(<4.17\) pg/ml; sIL-2R, \(0.04–0.85\) ng/ml; TNF-p75, \(2.0–5.5\) ng/ml; TNF-p55, \(0.4–1.7\) ng/ml.

† Analysis of covariance after adjusting for baseline values.

### Table 2. Differences in Cytokine Levels, Fat, FFM, and Weight Between Baseline and Final Evaluation in All Patients

<table>
<thead>
<tr>
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<th>Placebo</th>
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Notes: FFM = fat-free mass; MA = megestrol acetate.

† Analysis of covariance after adjusting for baseline values.
TNFR-p55 ($r = .42$); and between fat gain and reduction of TNFR-p75 ($r = -.41$) in the MA group (Table 5).

**Safety and Overall Survival**

A total of 69 patients (33 placebo and 36 MA patients) received at least one dose of study medication and qualified for the safety analysis. The number of patients who withdrew from the study during the treatment period was similar in the placebo and MA-treatment groups. Sixteen patients (eight in each treatment group) reported a total of 19 adverse events (8 in the placebo group and 11 in the MA group) during the 12 weeks of the study. There were no differences in infections during the trial in both groups ($p = .50$). There were no statistically significant differences between the MA and placebo groups or events that were clearly related to drug treatment.

**DISCUSSION**

In this predominantly male geriatric population with weight loss, there were no significant changes in cytokine levels between the MA and placebo groups after 12 weeks of treatment. However, weight gain did become significant after 12 weeks, and the reduction in cytokine levels after MA treatment correlated with improvement in weight, fat mass, and FFM. Weight gain itself appears to be associated with a reduction in levels of these cytokines. For example, MA treatment in cancer patients with wasting syndrome appears to be associated with a reduction in levels of cytokines and weight gain (28,29). We have postulated that the same holds true with geriatric patients with unexplained weight loss.

In the present study, weight gain itself appeared to be modestly correlated with a reduction in cytokine levels ($r = -.30$) in the overall patient population (Table 4). The correlation remained significant and the magnitude of the coefficients was higher in patients treated with MA (Table 5). Although the FFM gain was not significant with MA treatment, there was an inverse relationship between the reduction of cytokine levels and gain in FFM by 12 weeks. Fat gain also correlated with TNFR levels in the MA group as well. Such a relationship was not observed in the placebo group. Weight gain positively correlated with fat gain as measured by BIA ($r = .71$, $p = .0001$), FFM gain ($r = .68$, $p = .0001$), and body water ($r = .58$, $p = .0001$; Pearson correlation coefficient).

During the 3-month blinded follow-up period after discontinuing the study drug, we found that those patients who gained weight in the placebo group eventually lost the weight by the 5th month. Of the seven placebo patients who gained more than 4 lbs during the first 12 weeks of study, only three were able to maintain their new weight. However, those who gained weight in the MA-treatment group continued gaining or maintained their weight. We postulate that the weight gain in the placebo group was not lasting because without correcting the underlying pathophysiological problem (elevation of cytokines), they were not able to maintain their weight. In the MA group, however, the reduction of the cytokines possibly took months because there had to be a change in the underlying cytokine-generating condition before MA could be effective.

Another important physiological explanation for the delayed response comes from Roberts and colleagues (30) who investigated the effects of aging on body-energy regulation to determine the causes of unexplained weight loss in older individuals. They showed that older individuals take much longer to compensate for weight loss compared with younger individuals. They showed that older individuals take much longer to compensate for weight loss compared with younger individuals. They showed that older individuals take much longer to compensate for weight loss compared with younger individuals.
longer to change their “set point” for food intake. They found that aging may be associated with an impairment in the ability to control food intake following overeating or undereating. The precise mechanism of weight gain in the MA-treated patients is unclear, but may include a change in the set point for hunger and/or eating, induction of hyperphagia, suppression of catabolic effects, or other metabolic changes permitting more efficient use of food.

IL-6 is probably a marker of chronic stress in elderly persons, as suggested by Wilder (31). We have confirmed the observation of others that nursing home patients with weight loss have higher levels of IL-6 (32–36). We did not find sIL-2R to be elevated at the baseline as did Manousakkas and colleagues (37). Its reduction, however, was associated with weight gain. Of note was the fact that although the level of TNFR was not highly elevated at the baseline, weight gain itself was associated with reduced levels of TNFR. To our knowledge, this is the first report of a reduction in TNFR and sIL-2R that is associated with weight gain after treatment in a geriatric weight-loss population. We also confirmed that patients who did not gain weight (or reduce their cytokine levels) were those who had infections during the trial (p = .01).

Reductions in cytokine levels were highly correlated with one another (r = .39–.78, p ≤ .007; except sIL-2R to IL-6, r = .20). These findings suggest that the global reduction in levels of these cytokines may also contribute to reversal of the geriatric wasting syndrome, although the exact mechanism of MA treatment on weight gain, the reduction in cytokine levels, and the interaction of cytokines with one another are still not clear.

There are several limitations of this study. First, the cytokine levels in the follow-up period were not analyzed at precisely the time during which the weight gain became significant. Second, the serum levels of these cytokines were low and may not have reflected accurate tissue activity. Cytokine function in a paracrine fashion. Assays of serum activity may be inaccurate even when surrogate markers of their activity, such as TNF-receptor levels, are utilized. Release of cytokines from peripheral blood mononuclear cells may be a more accurate measure of their levels, rather than serum determination. Third, we did not assay the levels of IL-10 and IL-4, which have suppressive effects on these cytokines (TNF, IL-6, and IFN-γ). It would be interesting to study whether MA increases IL-10 or IL-4 levels. Another limitation may be that we used the BIA software equations provided by Rudolf J. Liedtke, which are based on a younger, healthy population. There will be some gain in accuracy and precision by using BIA equations designed for the elderly population, such as those of Deurenberg and colleagues (38) or Roubenoff and colleagues (39). In the current study, the small sample size was not sufficiently powered to show significance in weight gain or in cytokine changes during the initial 12-week treatment period. Last, the predominately male population in this study may not predict the effect of MA in a female nursing home population.

Despite these limitations, this study expands our knowledge of the correlation between cytokine reduction and associated weight, FFM, and fat gains after MA treatment in geriatric weight-loss patients. Confirmation of its effects in both genders in a larger multicenter trial is warranted. Further study of the safety of chronic treatment with MA will also be necessary.

Acknowledgments

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