Maastricht University

Effects of medroxyprogesterone acetate on food intake, body composition, and resting energy expenditure in patients with advanced, nonhormone-sensitive cancer: a randomized, placebo-controlled trial.

Document status and date:
Published: 01/01/1998

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

Effects of Medroxyprogesterone Acetate on Food Intake, Body Composition, and Resting Energy Expenditure in Patients with Advanced, Nonhormone-Sensitive Cancer

A Randomized, Placebo-Controlled Trial

Jean Paul F. H. A. Simons, M.D., Ph.D[1]
Annemie M. W. J. Schols, Ph.D.[1]
Janine M. J. Hoefnagels[2]
Klaas R. Westerterp, Ph.D.[3]
Guul P. M. ten Velde, Ph.D.[1]
Emiel F. M. Wouters, Ph.D.[1]

[1] Department of Pulmonology, University Hospital, Maastricht, The Netherlands.

[2] Department of Dietetics, University Hospital, Leiden, The Netherlands.

[3] Department of Human Biology, Maastricht University, Maastricht, The Netherlands.

BACKGROUND. Anorexia and cachexia are well-known sequelae of cancer that contribute to morbidity and mortality. In several studies in patients with non–hormone-sensitive tumors, synthetic progestogens were shown to exert beneficial effects on appetite and weight loss. The current study was undertaken to investigate the effects of medroxyprogesterone acetate (MPA) on food intake, body composition, and resting energy expenditure (REE).

METHODS. Fifty-four patients with non–hormone-sensitive cancer, generally characterized by substantial weight loss and hypermetabolism, received either MPA, 500 mg, or placebo twice daily for 12 weeks (double-blind study). Food intake was measured by dietary history, body composition was assessed by deuterium dilution (fat mass, fat-free mass), and REE was obtained by indirect calorimetry.

RESULTS. Compared with placebo, 12 weeks of MPA led to an increase in energy intake (between-group difference, 426 kcal/day; $P = 0.01$) that was significantly associated ($r = 0.68$, $P = 0.003$) with an increase in fat mass (between-group difference, 2.5 kg; $P = 0.009$). Fat-free mass was not significantly influenced. REE increased during MPA treatment: at 6 weeks, the between-group difference in change was 135 kcal/day ($P = 0.009$); after 12 weeks, this difference was 93 kcal/day ($P = 0.07$).

CONCLUSIONS. The authors conclude that MPA is able to stimulate increased food intake significantly and to reverse fat loss concomitantly in patients with non–hormone-sensitive cancer. *Cancer* 1998;82:553–60.
© 1998 American Cancer Society.

KEYWORDS: cancer, cachexia, therapy, medroxyprogesterone acetate, food intake, body composition, resting energy expenditure.

Substantial weight loss, eventually leading to cachexia, is a well-known complication of advanced stage cancer.[1] Metabolic disturbances (including hypermetabolism) and a food intake that is too low to meet metabolic needs are considered to be important contributing factors in its complex pathophysiology.[2–4] Because cachexia is associated with an unfavorable effect on morbidity and mortality,[5–7] several agents have been tested for their ability to improve cancer-related weight loss. Agents such as corticosteroids,[8,9] cyproheptadine,[10] and hydrazine sulfate,[11] however, have failed to show such properties in controlled human studies.

Synthetic progestogens—megestrol acetate and medroxyproges-

terone acetate (MPA)—have been shown to improve appetite and weight, independent of tumor response, when used in the treatment of disseminated breast carcinoma.[12,13] Subsequently, several placebo-controlled studies with these agents have been performed in patients with non–hormone-sensitive cancer.[14–19] In these studies, a beneficial influence was observed, with minimal side effects on appetite and (at least in a subgroup of patients) weight gain.

However, there is very little evidence from controlled studies as to whether improved appetite in these patients also results in an increase in food intake and whether the observed weight gain represents tissue mass and not just fluid retention, which is a reported side effect of synthetic progestogens.[15,18,20] To clarify these issues, we conducted a double-blind, placebo-controlled study in patients with advanced stage, non–hormone-sensitive cancer to investigate the effects of MPA on food intake and body composition. The effects of MPA on resting energy expenditure (REE) were also assessed.

PATIENTS AND METHODS
Patients
The present study was performed on a subgroup of patients participating in a multicenter study investigating the effects of MPA on appetite, weight, and quality of life in advanced stage, non–hormone-sensitive cancer.[19] The subgroup was formed by patients recruited at the University Hospital Maastricht, The Netherlands. Patients with the following histologically or cytologically diagnosed, non–hormone-sensitive, incurable malignancies were considered eligible: non-small cell carcinoma of the lung; mesothelioma; carcinoma of the digestive tract or pancreas; carcinoma of the kidney, bladder, or ureter; and disseminated carcinoma of unknown origin. All patients were required to have a Karnofsky performance status score ≥60%. Exclusion criteria were as follows: brain metastases; thromboembolic events during the past year; poorly controlled hypertension or heart failure; diabetes mellitus or thyroid disease; the use of oral or parenteral corticosteroids, androgens, progestogens, anticonvulsants, or rifampicin; jaundice; serum creatinine level > 200 μmol/L; enteral or parenteral tube feedings; and known malabsorption or mechanical obstruction of the digestive tract. The protocol was in accordance with the Helsinki Declaration of 1975, as revised in 1983, and was approved by the institutional review board for human research of the University Hospital Maastricht. Written informed consent was obtained from all patients.

Study Design
Eligible patients were randomized (block randomization in permutation blocks of four) between MPA (Farlutal; Pharmacia, Woerden, The Netherlands), 500 mg twice daily, or placebo twice daily. Stratification was applied for primary disease site (lung vs. other). The design of the study was double-blind with a treatment duration of 12 weeks. All patients were instructed to take one tablet before breakfast and one tablet before the evening meal. Food intake, body composition, and REE were assessed before the start of treatment (t = 0) as well as at 6 weeks (t = 6) and 12 weeks (t = 12) thereafter.

Food Intake
Energy, protein, fat, and carbohydrate intake were obtained by using the dietary history method with a reference period of 30 days.[21] All interviews were performed by the same, trained dietician. The Dutch food composition table was used for the calculation of energy intake (EI) and macronutrient intake.[22]

Body Composition
According to a two-compartment body composition model, the human body can be divided into fat mass (FM) and fat-free mass (FFM). In the present study, FFM was assessed by deuterium dilution.[23,24] The following protocol was used. On the evening before each visit to the hospital, at ≈23 hours, all patients drank a weighted dose of ≈4.00 g deuterium (99.84 atom percent excess) in 50 ml water. Then the bottle was rinsed once with ≈50 ml tap water, which the patients also drank. Thereafter, patients had to refrain from eating and drinking. They were asked to void at least once at home before coming to the hospital. A urine sample was taken before and 10 hours after drinking the deuterium water. Deuterium was measured in duplicate in these two samples by using an isotope ratio-mass spectrometer (Aqua Sira; VG Isogas, Cheshire, UK).[25] Comparison of the duplicate measurements showed a precision >99%. Total body water (TBW) was calculated by dividing the measured volume of distribution of deuterium by 1.04, thereby correcting for the exchange of deuterium with nonaqueous hydrogen.[23] The use of this test protocol with an overnight equilibration period of 10 hours has been extensively validated in our laboratory.[26] It was shown that TBW assessed by using this protocol corresponds very well (bias 1%) with TBW derived from hydrodensitometry.[26] FFM was calculated by dividing the measured TBW by 0.73, the assumed hydration coefficient of the FFM in normal-weight healthy individuals.[27] FM was calculated by subtracting FFM from body weight.

Resting Energy Expenditure

REE was assessed by indirect calorimetry by using a ventilated hood system (Oxycon β; Mijnhardt, Bunnik, The Netherlands). After an overnight fast, CO_2 production and O_2 consumption were measured at complete rest during a period of 20 minutes. REE was calculated by using the abbreviated Weir formula[28] The equipment was calibrated at the start of each experiment. The precision of the system was checked monthly by burning methanol with a theoretical respiratory quotient of 0.667 after complete combustion. Further details on the technique used in our laboratory have been described elsewhere.[29] To document hypermetabolism, REE was compared (after adjustment for differences in sex and FFM) with REE measured in a group of healthy individuals (mean age, 70 ± 5 years). This reference group, recently assessed in our laboratory, was characterized by an REE of 1623 ± 192 kcal/day in males (n = 16) and of 1271 ± 108 kcal/day in females (n = 9).

Statistical Analysis

All patients finishing the 12-week study were analyzed. Group means were compared by Student's t test. Differences in categoric variables were analyzed by chi-square test with Yates' continuity correction or Fisher's exact test, when appropriate. Longitudinal changes were analyzed within and between groups by means of a repeated measures analysis capable of dealing with randomly missing values.[30,31] This analysis yields estimated values per group for each measurement time, adjusted for missing values, and tests for changes from t = 0 to t = 6 and from t = 0 to t = 12. Because FFM is the body compartment that mainly determines the level of metabolic activity, FFM was used as a covariable in all REE analyses. Pearson's product-moment correlation coefficients were used to evaluate linear relationships between variables. The repeated measures analysis was performed by using BMDP 5V.[31] For all other analyses, SPSS/PC+ (version 6.0 for Windows; SPSS, Chicago, IL) was used. Statistical significance was determined at the 5% level, two-sided. Unless otherwise stated, results are given as score mean ± standard deviation (SD).

RESULTS

Fifty-four eligible patients were randomized. Twenty-seven patients were assigned to each treatment group, and 33 patients (18 MPA patients, 15 placebo patients) completed the 12-week study. The reasons for sample attrition were as follows: death or physical deterioration (three MPA patients, four placebo patients), side effects (four placebo patients, all gastrointestinal discomfort), refusal to continue (three placebo patients),

protocol violation (two MPA patients, one placebo patient), mechanical obstruction of the digestive tract (three MPA patients), and sigmoid perforation and peritonitis (one MPA patient).

Table 1 shows the baseline characteristics of patients who entered the study and patients who completed the study, stratified by study arm. There were no significant differences between the treatment groups. The majority of patients were male, the predominant malignancy was nonsmall cell lung carcinoma, the vast majority of patients had distant metastases, and none of the patients was concurrently treated with chemotherapy. The majority of patients were characterized by substantial involuntary weight loss. Sixty-five percent of eligible patients had lost more than 5% of their preillness weight, and 20% of the subjects had lost 0–5%. This prestudy weight loss was also demonstrated by the fact that the average body weight was approximately 100% of ideal body weight,[32] whereas in a healthy Dutch elderly population body weight is normally more than 110% of ideal weight in males and more than 120% of ideal weight in females.[33] In comparison with the healthy reference group, the patients entered onto the study were significantly hypermetabolic ($P = 0.02$).

Figure 1 shows the observed changes in food intake for both treatment arms. Because food intake data were not available in 1 placebo patient, 14 placebo patients and 18 MPA patients were used in the analysis. At t = 12, a mean increase in EI of 418 kcal/day was found in the MPA group versus no change in the placebo group (between-group difference, 425 kcal/day; $P = 0.01$). This increase was the result of a significantly improved intake of protein, fat, and carbohydrates.

Figure 2 shows the changes in body composition. All subjects reaching t = 12 were used in the analysis. During the study, peripheral edema developed in four MPA patients and in one placebo patient. At t = 12, a mean gain in FM of 1.0 kg was observed in MPA patients versus a fat loss of 1.5 kg in the placebo group (between-group difference, $P = 0.009$). An increase in FM was seen in 71% of MPA patients, whereas in the placebo group an FM increase was observed in 20% of patients (between-group difference, $P = 0.01$). FFM increased by 1.0 kg in the MPA group ($P = 0.04$) and by 0.4 kg in the placebo group. However, half the average FFM increase in the MPA group was accounted for by edema developing in the subjects. When these patients were excluded from FFM analysis, the remaining mean within-group change (+0.5 kg) lost statistical significance.

Figure 3 shows that the MPA-related changes in

TABLE 1
Baseline Characteristics of Eligible and Assessable Patients Stratified by Treatment Group[a]

	Eligible		Assessable[b]	
	MPA (n = 27)	Placebo (n = 27)	MPA (n = 18)	Placebo (n = 15)
Sex (%)				
Male	74	78	78	87
Female	26	22	22	13
Age (yrs)	66 ± 10	65 ± 8	68 ± 8	67 ± 7
Tumor type (%)				
Nonsmall cell lung carcinoma	63	59	61	73
Digestive tract carcinoma	19	7	22	7
Other	19	34	17	20
Histology (%)				
Adenocarcinoma	37	52	33	47
Squamous cell	22	37	22	47
Undifferentiated large cell	37	11	39	7
Other	4	0	6	0
Metastases (%)	89	93	89	93
Karnofsky performance status				
(%)	76 ± 9	74 ± 9	77 ± 9	77 ± 10
Chemotherapy (%)	0	0	0	0
Edema (%)	4	11	0	0
Appetite (0–10)[c]	6.2 ± 2.8	6.9 ± 2.5	7.1 ± 2.5	6.9 ± 2.8
Weight loss (kg)[d]	5.6 ± 7.2	7.1 ± 5.7	5.0 ± 6.4	4.8 ± 5.1
Weight los (%)[d]	7.4 ± 9.6	9.9 ± 7.9	6.9 ± 8.6	6.5 ± 6.8
Weight (kg)	65.3 ± 8.3	65.2 ± 10.6	65.1 ± 9.2	69.4 ± 10.2
Height (m)	1.68 ± 0.09	1.69 ± 0.08	1.68 ± 0.08	1.70 ± 0.07
Body mass index (kg/m^2)	23.1 ± 2.3	22.9 ± 4.1	23.0 ± 2.3	24.2 ± 4.0
WT/IBW (%)[e]	101 ± 11	100 ± 17	101 ± 11	106 ± 17
Fat-free mass (kg)	49.8 ± 9.4	49.0 ± 6.5	49.4 ± 9.4	52.0 ± 6.0
Fat mass (kg)	15.5 ± 6.3	16.2 ± 8.3	15.8 ± 5.1	17.3 ± 7.2
Energy intake (kcal/day)	2267 ± 754	2151 ± 610	2320 ± 756	2025 ± 529
REE (kcal/day)	1639 ± 276	1661 ± 234	1659 ± 285	1699 ± 235

MPA: medroxyprogesterone acetate; REE: resting energy expenditure.

[a] Scores expressed as mean ± SD or percentage.

[b] Twelve-week study completed.

[c] Appetite expressed on a 0–10 numeric rating scale, 0 indicating absolutely no appetite and 10 indicating an extremely good appetite.

[d] Weight in relation to preillness weight.

[e] Body weight expressed as percentage of ideal body weight.

FM were significantly correlated with changes in EI (r = 0.68, P = 0.003).

In Figure 4, the observed changes in REE are show for both treatment groups. Because REE data were not available in 2 MPA patients (technical reasons) and in 1 placebo patient (claustrophobia), 14 placebo patients and 16 MPA patients were used in the analysis. At t = 6, a mean increase in REE of 65 kcal/day was observed in the MPA group versus a decrease of 70 kcal/day in the placebo group (between-group difference, 135 kcal/day; P = 0.009). At t = 12, the between-group difference was 93 kcal/day (P = 0.07).

DISCUSSION
Substantial weight loss, eventually leading to cachexia, is thought to play an important role in cancer-related morbidity and mortality.[5–7] Previous studies have shown that this weight loss is the result of a combined wasting of FM and body cell mass,[3,34] the latter being the body compartment containing most of the tissues (muscle, organs) that are vital to normal functioning of the body.[27] Several placebo-controlled studies in patients with non–hormone-sensitive cancer reported a beneficial influence of synthetic progestogens on appetite and (at least in a subgroup of patients) weight.[14–19] In an open, non-controlled study with megestrol acetate in 12 weight-stable, nonanorectic patients with breast carcinoma (11 females, 1 male), Loprinzi et al[35] reported that in those patients who gained weight (n = 7), the weight gain was predominantly the result of an increase in dual-energy X-ray absorptiometry (DEXA)-derived fat mass. In a 1-week, placebo-con-
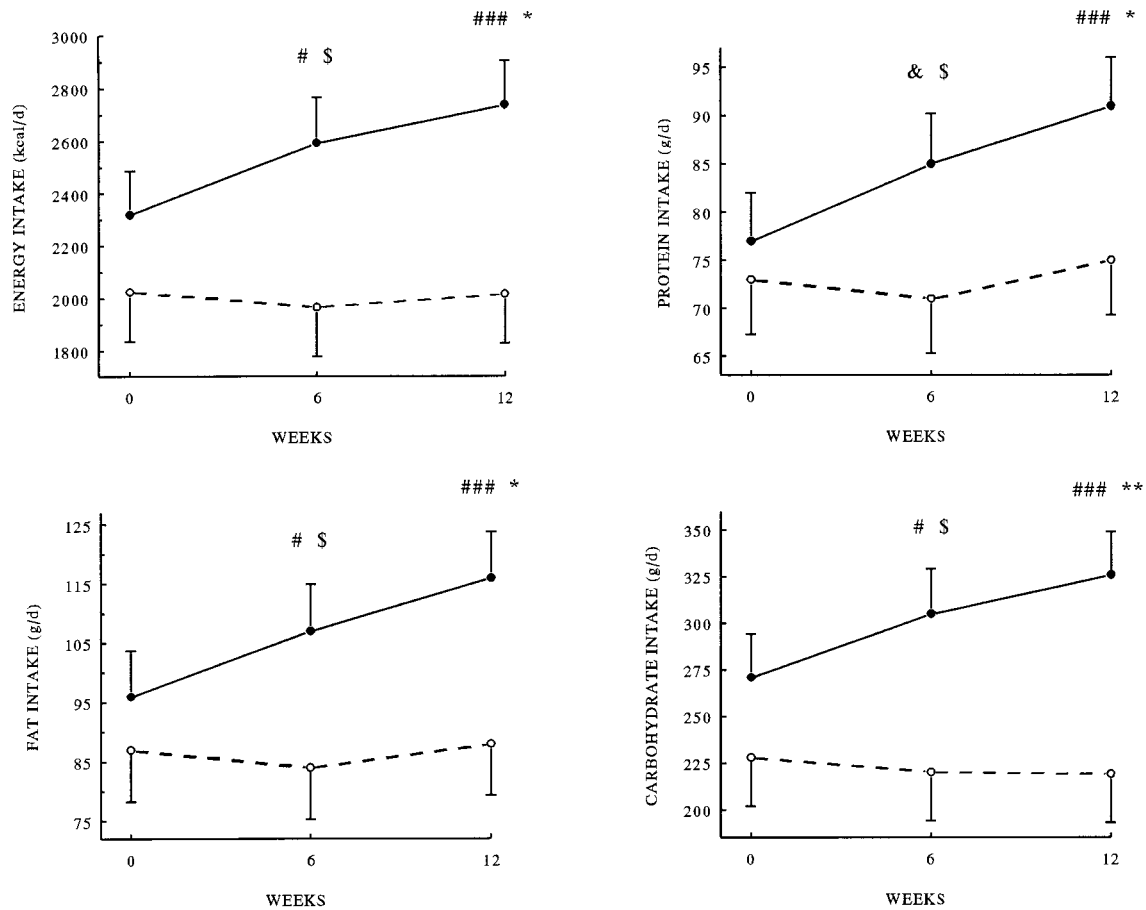
FIGURE 1. Intake of energy, protein, fat, and carbohydrates (mean values and SEM) at baseline and after 6 weeks and 12 weeks of treatment in the MPA group (solid lines) and placebo group (dashed lines). P values for within-group changes from baseline are indicated as follows: ###, $P < 0.001$; #, $P < 0.05$; &, $P < 0.1$. P values for between-group differences in changes from baseline are indicated as follows: **, $P < 0.01$; *, $P < 0.05$; $, $P < 0.1$.
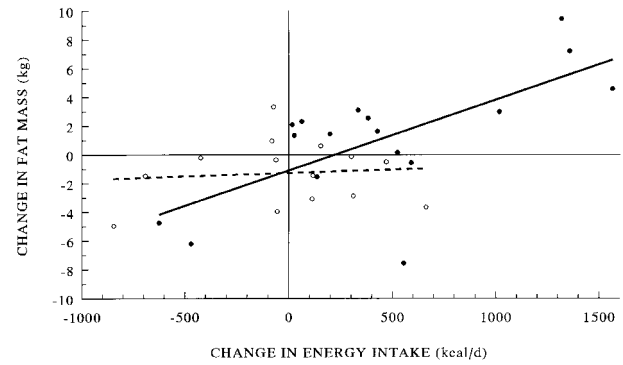
trolled, cross-over study, Bruera et al[14] observed a statistically significant beneficial effect of megestrol acetate on EI. To our knowledge, no other cancer studies (particularly placebo-controlled studies with a relatively long treatment duration) have been performed to study the effects of synthetic progestogens on energy balance and body composition. In two placebo-controlled studies of patients with cachexia due to AIDS, megestrol acetate was reported to increase caloric intake.[36,37] With respect to (bioelectrical impedance analysis-derived) body composition, one of these studies showed a beneficial effect of megestrol acetate on FM, whereas the other also found a beneficial effect on lean body mass. However, the latter finding was contradicted by the fact that there was no significant change in TBW. In both studies, a relatively high daily dose of 800 mg megestrol acetate was used (160 mg megestrol acetate is assumed to be equivalent to 1000 mg MPA[38]).

The present study was designed to investigate the effects of a 12-week treatment with MPA (500 mg twice daily) on food intake, body composition, and energy expenditure in non–hormone-sensitive cancer. The study was performed in a randomized, placebo-controlled fashion in a subgroup of patients participating in a multicenter study investigating the effects of MPA on appetite, weight, and quality of life. In the latter study, a significant MPA-related beneficial effect on both appetite and weight was observed.[19] The results of the present study indicate that in these patients, generally characterized by weight loss and hypermetabolism, the increase in appetite actually leads to a significant increase in energy, protein, fat, and carbohydrate intake, and that concomitantly a reversal of ongoing fat loss can be established. Although an edema-related increase in FFM was observed in some MPA-treated patients, FFM changes seemed to generally play a minor role (if any) in MPA-induced weight

FIGURE 3. Correlation between changes in energy intake and changes in fat mass in the MPA patients (filled circles, solid line; r = 0.68; *P* = 0.003) and placebo patients (open circles, dashed line; r = 0.09; *P* = 0.77) after 12 weeks of treatment.
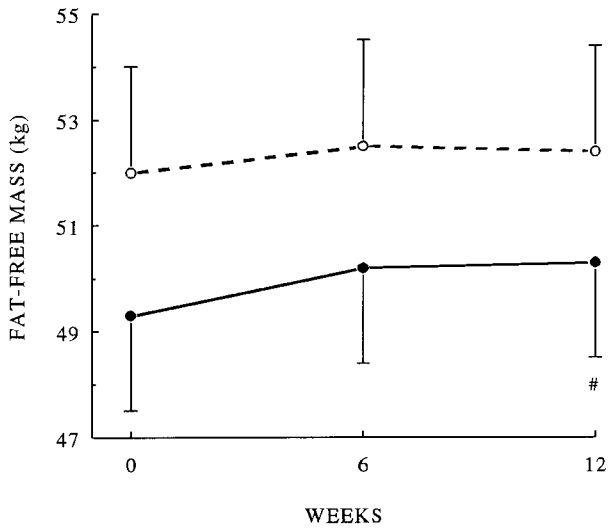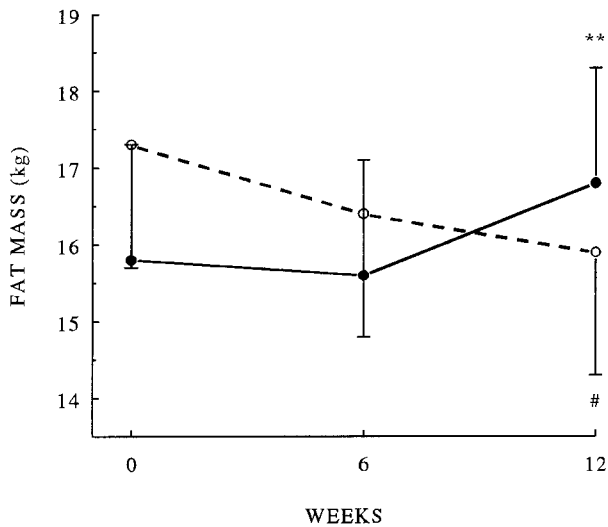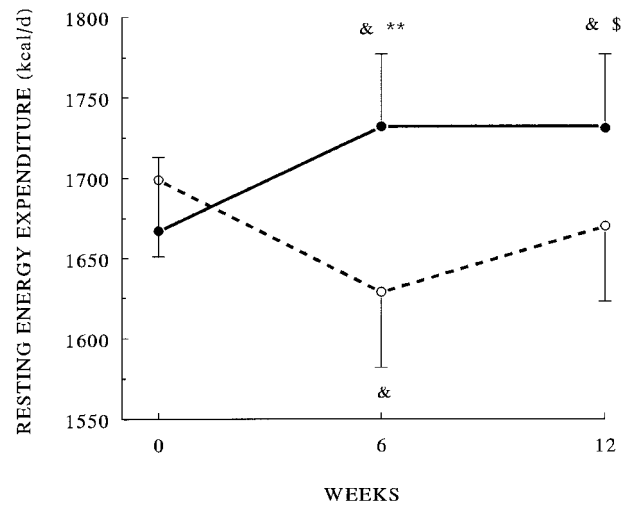

FIGURE 2. Fat mass and fat-free mass (mean values and SEM) at baseline and after 6 weeks and 12 weeks of treatment in the MPA group (solid lines) and placebo group (dashed lines). *P* values for within-group changes from baseline are indicated as follows: #, *P* < 0.05. *P* values for between-group differences in changes from baseline are indicated as follows: **, *P* < 0.01.

FIGURE 4. Resting energy expenditure (mean values and SEM) at baseline and after 6 weeks and 12 weeks of treatment in the MPA group (solid line) and placebo group (dashed line). *P* values for within-group changes from baseline are as follows: &, *P* < 0.1. *P* values for between-group differences in changes from baseline are as follows: **, *P* < 0.01; $, *P* < 0.1.

change. Although TBW-derived changes in FFM do not by definition represent changes in body cell mass, this finding might indicate that a 12-week treatment with MPA fails to improve this functionally important body compartment. In theory, a testosterone-lowering effect of MPA might explain this negative finding in our predominantly male study population.[39] However, the small number of assessable MPA-treated female patients (three edema-free subjects) precluded further elaboration of this hypothesis. Finally, in addition to its effects on food intake and FM, the use of MPA was

associated with a (further) increase in REE. Although the explanation for this finding remains speculative (a direct metabolic effect of the agent?), the induced improvement of EI was obviously sufficient to achieve a positive energy balance. A possible limitation of the present study was the fact that 40% of the eligible patients were unassessable due to premature dropout. This is a common and unavoidable problem in clinical trials in advanced stage cancer, particularly in trials with relatively long treatment durations.

Some methodologic aspects of the current study

merit further discussion. First, body composition was derived from TBW, measured by deuterium dilution. When using this method, FFM is calculated by dividing the measured TBW by 0.73, the assumed hydration coefficient of the FFM in normal-weight healthy individuals.[27] FM is subsequently calculated by subtracting FFM from body weight. To our knowledge, limited data are available in the literature on the hydration coefficient of the FFM in normal-weight or underweight cancer patients. However, in a group of 20 male lung carcinoma patients with a mean body mass index of 20.8 ± 2.8 kg/m^2 (range, 15.9–24.9 kg/m^2) recently analyzed in our laboratory by DEXA-scanning and deuterium dilution, the mean hydration coefficient was 0.73 ± 0.03 (range, 0.68–0.79) and was not correlated with body mass index ($r = 0.16$, $P = 0.51$) (unpublished observations). Nevertheless, because fluid retention occurred in some patients, changes in the hydration coefficient during the follow-up period could have introduced some bias in the MPA group toward an overestimation of FFM changes and an underestimation of FM changes. If this phenomenon indeed played a role, it would strengthen rather than weaken the conclusions drawn from the current results.

Second, food intake was assessed by the dietary history technique, a method that has recently been validated against measurements of total energy expenditure using whole-body indirect calorimetry.[40] In this study performed in elderly women, an average underestimation of EI of 12% was reported, a finding that also applies to most other self-reported food intake assessment methods.[41] For the present study (which attempted to compare within-group changes between two groups in a randomized, placebo-controlled fashion), however, it was more important that several earlier studies reported very good reproducibility of the dietary history method (see review by Block[21]).

The mechanism of action of synthetic progestogens in the treatment of cancer-related weight loss is still obscure. Synthetic progestogens obviously interfere with the complex regulation of food intake,[42,43] but on what level (hypothalamic, neuroendocrine, gut) is unclear. Furthermore, it is not known whether these agents also have specific direct effects on metabolism. In a study in rats, megestrol acetate has been shown to stimulate the hypothalamic synthesis, transport, and release of neuropeptide Y,[44] a potent stimulator of appetite.[45] In another in vitro study with megestrol acetate, a direct stimulation of adipocyte differentiation was reported.[46]

In conclusion, the present study demonstrates that the synthetic progestogen MPA has the potential to increase food intake and to concomitantly reverse fat wasting in weight-losing patients with cancer. It remains to be determined, however, whether protein wasting can also be influenced by MPA as particularly preservation of protein mass can be expected to interfere beneficially with morbidity and mortality in the longer term.

REFERENCES

1. Theologides A. Cancer cachexia. *Cancer* 1979;43(suppl 5):2004–12.
2. Tisdale MJ. Cancer cachexia. *Anticancer Drugs* 1993;4:115–25.
3. Nelson KA, Walsh D, Sheehan FA. The cancer anorexia-cachexia syndrome. *J Clin Oncol* 1994;12:213–25.
4. Staal-van den Brekel AJ, Schols AM, ten Velde GP, Buurman WA, Wouters EF. Analysis of the energy balance in lung cancer patients. *Cancer Res* 1994;54:6430–3.
5. Warren S. The immediate causes of death in cancer. *Am J Med Sci* 1932;184:610–5.
6. DeWys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. *Am J Med* 1980;69:491–7.
7. Costa G, Bewley P, Aragon M, Siebold J. Anorexia and weight loss in cancer patients. *Cancer Treat Rep* 1981;65(suppl 5):3–7.
8. Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Corticosteroid therapy of preterminal gastrointestinal cancer. *Cancer* 1974;33:1607–9.
9. Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep* 1985;69:751–4.
10. Kardinal CG, Loprinzi CL, Schaid DJ, Hass AC, Dose AM, Athmann LM, et al. A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. *Cancer* 1990;65:2657–62.
11. Chlebowski RT, Bulcavage L, Grosvenor M, Oktay E, Block JB, Chlebowski JS, et al. Hydrazine sulfate influence on nutritional status and survival in non-small-cell lung cancer. *J Clin Oncol* 1990;8:9–15.
12. Cavalli F, Goldhirsch A, Jungi F, Martz G, Mermillod B, Schäfer P, et al. Randomized trial of low-versus-high-dose medroxyprogesterone acetate in the treatment of postmenopausal patients with advanced breast cancer. In: Pellegrini A, Robustelli Della Cuna G, editors. Role of medroxyprogesterone in endocrine-related tumors. vol. 3. New York: Raven Press, 1984:79–89.
13. Tchekmedyian NS, Tait N, Moody M, Aisner J. High-dose megestrol acetate: a possible treatment for cachexia. *JAMA* 1987;257:1195–8.
14. Bruera E, Macmillan K, Kuehn N, Hanson J, MacDonald RN. A controlled trial of megestrol acetate on appetite, caloric intake, nutritional status, and other symptoms in patients with advanced cancer. *Cancer* 1990;66:1279–82.
15. Loprinzi CL, Ellison NM, Schaid DJ, Krook JE, Athmann LM, Dose AM, et al. Controlled trial of megestrol acetate for the treatment of cancer anorexia and cachexia. *J Natl Cancer Inst* 1990;82:1127–32.
16. Tchekmedyian NS, Hickman M, Siau J, Greco FA, Keller J, Browder H, et al. Megestrol acetate in cancer anorexia and weight loss. *Cancer* 1992;69:1268–74.
17. Feliu J, Gonzalez-Baron M, Berrocal A, Artal A, Ordonez A, Garrido P, et al. Usefulness of megestrol acetate in cancer cachexia and anorexia. *Am J Clin Oncol* 1992;15:436–40.

18. Rowland KM Jr., Loprinzi CL, Shaw EG, Maksymiuk AW, Kuross SA, Jung SH, et al. Randomized double-blind placebo-controlled trial of cisplatin and etoposide plus megestrol/placebo in extensive-stage small-cell lung cancer: a north central cancer treatment group study. *J Clin Oncol* 1996;14:135–41.

19. Simons JP, Aaronson NK, Vansteenkiste JF, ten Velde GP, Muller MJ, Drenth BM, et al. The effects of medroxyprogesterone acetate on appetite, weight and quality of life in advanced stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. *J Clin Oncol* 1996;14:1077–84.

20. Tchekmedyian NS, Tait N, Abrams J, Aisner J. High-dose megestrol acetate in the treatment of advanced breast cancer. *Semin Oncol* 1988;15(suppl 1):44–9.

21. Block G. A review of validations of dietary assessment methods. *Am J Epidemiol* 1982;115:492–505.

22. NEVO table. Stichting Nederlands voedingsstoffenbestand's gravenhage. The Netherlands: Voorlichtingsbureau voor de Voeding, 1990.

23. Schoeller DA, van Santen E, Peterson DW, Dietz W, Jaspan J, Klein PD. Total body water measurement in humans with ^{18}O and ^{2}H labeled water. *Am J Clin Nutr* 1980;33:2686–93.

24. van der Kooy K, Leenen R, Deurenberg P, Seidell JC, Westerterp KR, Hautvast JG. Changes in fat-free mass in obese subjects after weight loss: a comparison of body composition measures. *Int J Obes Relat Metab Disord* 1992;16:675–83.

25. Barrie A, Coward WA. A rapid analytical technique for the determination of energy expenditure by the doubly labelled water method. *Biomed Mass Spectrom* 1985;12:535–41.

26. Westerterp KR, Wouters L, van Marken Lichtenbelt WD. The Maastricht protocol for the measurement of body composition and energy expenditure with labeled water. *Obes Res* 1995;3(1 suppl):49–57.

27. Forbes GB. Techniques for estimating body composition. In: Forbes GB, editor. Human body composition. New York: Springer-Verlag, 1987:5–100.

28. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol* 1949;109:1–9.

29. Schols AM, Schoffelen PF, Ceulemans H, Wouters EF, Saris WH. Measurement of resting energy expenditure in patients with chronic obstructive pulmonary disease in a clinical setting. *JPEN* 1992;16:364–8.

30. Jennrich RI, Schluchter MD. Unbalance repeated-measures models with structured covariance matrices. *Biometrics* 1986;42:805–20.

31. Dixon WJ, chief editor. BMDP statistical software, to accompany the 7.0 software release. Berkeley: University of California Press, 1992.

32. Metropolitan Life Insurance Company. New weight standards for men and women. *Stat Bull Metrop Life Found* 1983;64:1–4.

33. Löwik MR, Westenbrink S, Meulmeester JF, van de Berg H, Hulshof KF, Kistemaker C, et al. Onderzoek naar de voeding en voedingstoestand van zelfstandig wonende mensen van 65 tot 80 jaar. *Voeding* 1987;48:177–91.

34. Fearon KC, Preston T. Body composition in cancer cachexia. *Infusionstherapie* 1990;17(suppl 3):63–6.

35. Loprinzi CL, Schaid DJ, Dose AM, Burnham NL, Jensen MD. Body-composition changes in patients who gain weight while receiving megestrol acetate. *J Clin Oncol* 1993;11:152–4.

36. Oster MH, Enders SR, Samuels SJ, Cone, LA, Hooton TM, Browder HP, et al. Megestrol acetate in patients with AIDS and cachexia. *Ann Intern Med* 1994;121: 400–8.

37. Von Roenn JH, Armstrong D, Kotler DP, Cohn DL, Klimas NG, Tchekmedyian NS, et al. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med* 1994;121:393–9.

38. Willemse PH, van der Ploeg E, Sleijfer DT, Tjabbes T, van Veelen H. A randomized comparison of megestrol acetate (MA) and medroxyprogesterone acetate (MPA) in patients with advanced breast cancer. *Eur J Cancer* 1990;26:337–43.

39. Engelson ES, Pi-Sunyer FX, Kotler DP. Effects of megestrol acetate therapy on body composition and circulating testosterone concentrations in patients with AIDS [letter]. *AIDS* 1995;9:1107–8.

40. Visser M, de Groot LC, Deurenberg P, van Staveren WA. Validation of dietary history method in a group of elderly women using measurements of total energy expenditure. *Br J Nutr* 1995;74:775–85.

41. Sawaya AL, Tucker K, Tsay R, Willett W, Saltzman E, Dallal GE, et al. Evaluation of four methods for determining energy intake in young and older women: comparison with doubly labelled water measurements of total energy expenditure. *Am J Clin Nutr* 1996;63:491–9.

42. Dewys WD. Anorexia as a general effect of cancer. *Cancer* 1979;43(suppl 5):2013–9.

43. Rohner-Jeanrenaud F. A neuroendocrine reappraisal of the dual-centre hypothesis: its implications for obesity and insulin resistance. *Int J Obes Relat Metab Disord* 1995;19:517–34.

44. McCarthy HD, Crowder RE, Dryden S, Williams G. Megestrol acetate stimulates food and water intake in the rat: effects on regional hypothalamic neuropeptide Y concentrations. *Eur J Pharmacol* 1994;265:99–102.

45. Dryden S, Frankish H, Wang Q, Williams G. Neuropeptide Y and energy balance: one way ahead for the treatment of obesity? *Eur J Clin Invest* 1994;24:293–308

46. Hamburger AW, Parnes H, Gordon GB, Shantz LM, O'Donnell KA, Aisner J. Megestrol acetate-induced differentation of 3T3-L1 adipocytes in vitro. *Semin Oncol* 1988;15(suppl 1):76–8.