# Megestrol Acetate Therapy and Anorexia In Patients With Chronic Kidney Disease Undergoing Maintenance Dialysis

**Philippa Norton Feiertag, MEd, RD, LD**
*Clinical Information Specialist*
*Clinical Computing, Inc., Cincinnati, Ohio.*
*Email: Philippa.Feiertag@fuse.net.*

**This article has been approved for 1.5 CPE units and the CPE insert can be accessed in the Members Only Section of the website from the CPE Inserts link.**

Anorexia, defined as the loss of desire to eat, occurs frequently in patients with chronic kidney disease (CKD) undergoing maintenance dialysis therapy and contributes to kidney wasting disease (1,2). A recent systematic review of 60 studies of symptom occurrence in patients with CKD on dialysis revealed a mean prevalence of 49% for anorexia (3).

Hemodialysis (HD) patients who report decreased appetite have lower protein intake, hemoglobin levels, and quality of life scores. They also have higher levels of pro-inflammatory cytokines compared with patients reporting normal appetite (4,5). Poor performance of usual activities has been attributed to deficits in protein and energy intake as well (6). More importantly, CKD patients with poor appetite and lower dietary protein intake have higher hospitalization and death rates than those with better appetite and protein intake (4,7-10).

CKD patients with anorexia require aggressive intervention to improve their nutritional status and quality of life while decreasing their risk for morbidity and mortality. Intervention often involves use of high-density nutrition supplements to increase calorie and protein intake. However, there is evidence that nutrition supplementation administered orally or in dialysate may not definitively improve nutritional status in patients undergoing maintenance dialysis therapy (11). In addition, few of these studies have been directed to determine the impact of nutrition supplements on rates of morbidity and mortality in this population (12,13).

Pilot studies with recombinant human growth hormone (rHGH), insulin-like growth factor-1 (IGF-1), and androgen therapy have shown anabolic effects in adult dialysis patients (14-19). However, administration of these agents is expensive and side effects may be serious (20). Studies involving patients with cancer and acquired immunodeficiency syndrome (AIDS) have shown increased appetite, weight gain and improved quality of life following therapy with the progestational agent megestrol acetate (21-24). Of particular interest is the finding that progestational agents appear to decrease the levels of proinflammatory cytokines associated with anorexia and cachexia (25). For these reasons, there is increased attention to the potential therapeutic effects of megestrol acetate in patients with CKD undergoing maintenance dialysis therapy. This article will examine the association between proinflammatory cytokines and anorexia in CKD, and review studies of megestrol therapy in this population.

## Proinflammatory Cytokines and Anorexia

Food intake is regulated by neural and chemical signals transmitted to the hypothalamus in the brain. These signals originate from the gastrointestinal tract, liver, fat stores and circulating nutrients (5). Within the hypothalamus, catecholamine and serotonin pathways regulate food intake via the feeding center located in the lateral hypothalamus, and the satiety center in the ventromedial hypothalamus. Reduced food intake is associated with increased serotonin activity, which is synthesized from the amino acid tryptophan.

In patients with cancer, increased availability of tryptophan to the brain, and subsequent serotonin synthesis, has been implicated in the development of anorexia (26). Furthermore, interleukin 1 beta (IL-1 beta) and other cytokines released from malignant tissue may act directly on the satiety center to suppress food intake (27).

There is evidence to suggest that similar mechanisms may suppress appetite in patients with CKD (28). In patients undergoing maintenance dialysis therapy, an amino acid imbalance has been identified in anorexia. This imbalance is characterized by low concentrations of large

➡

neutral and branched chain amino acids in cerebrospinal fluid, which allows high levels of tryptophan to cross the blood-brain barrier and therefore increases serotonin synthesis (29).

High cytokine levels have been identified in patients with CKD undergoing maintenance HD and peritoneal dialysis (PD). Findings from one study suggest that the HD procedure may stimulate production of tumor necrosis factor (TNF) by peripheral blood mononuclear cells (PBMC) (30). High levels of TNF and interleukin-18 (IL-18) have also been detected in PD patients (31). Exogenously administered TNF is known to elicit symptoms of infection, including anorexia, and poor appetite in HD patients is associated with higher serum concentrations of interleukin-6 (IL-6) (32,33). These studies collectively may explain why cytokine-mediated anorexia in patients with CKD is resistant to hypercaloric feeding in the form of nutrition supplements.

## Megestrol Acetate Therapy

Megestrol acetate was originally used in the treatment of metastatic breast and endometrial cancers. Increased appetite and body weight were frequent side effects of this therapeutic regimen, resulting in its application to treat malnutrition inpatients with cancer and AIDS (34). More recently, the use of megestrol acetate as a therapeutic agent for malnutrition has been investigated in geriatric patients.

In one study, 69 nursing home patients with a weight loss ≥ 5% of usual body weight over the previous 3 months or with body weight 20% below their ideal weight were randomly assigned to receive megestrol acetate oral suspension (800 mg/day) or placebo for 12 weeks (35). Improvements in body weight, fat mass and fat free mass in the treatment group at 12 weeks were correlated with a reduction in cytokine levels. Reduction in cytokines after megestrol acetate therapy also correlated with improvements in appetite, albumin and prealbumin levels, and quality of life (36).

*Studies on megestrol acetate in patients undergoing maintenance dialysis therapy show mixed results.*

*These studies collectively indicate that small doses of megestrol acetate (up to 400 mg/day) may be effective and safe for treating anorexia and improving nutritional status in patients undergoing maintenance dialysis therapy. However, additional placebo-controlled studies with larger patient populations are needed to confirm these findings, and the impact of megestrol acetate on morbidity and mortality rates should also be determined.*

Studies on megestrol acetate in patients undergoing maintenance dialysis therapy show mixed results, and findings from these studies are summarized in Table 1. In a placebo-controlled trial, 160 mg megestrol acetate daily had no effect on serum albumin or lean body mass in a small group of HD patients (37). However, a small group of dialysis patients (4 on HD and 12 on PD) with persistent hypoalbuminemia (serum albumin <3.5 gm/dl for 2 consecutive months) treated with a low dose of 20 mg megestrol acetate twice daily showed a mean increase in serum albumin from 2.7±0.1 to 3.0±0.2 gm/dl after one month (38). Patients in this study who responded to megestrol acetate also reported improved appetite. Neither of these studies addressed the impact of megestrol acetate on dietary intake.

A case study of safety and efficacy of moderate doses of megestrol acetate in a male maintenance HD patient evaluated body weight, body composition, dietary intake, appetite, nutrition-related serum chemistries and quality of life as outcome measures (39). The patient had HIV nephropathy with poor appetite and a 3 kg unintentional weight loss over a 3 month period prior to the start of the study. Treatment with megestrol acetate was initiated at 320 mg/day for 12 weeks. Since dry weight was unchanged, the dose was increased to 440 mg/day at week 13 and to 560 mg/day at week 20. After 24 weeks, the patient reported improved appetite, and energy and protein intake increased. The patient gained little body weight (0.5 kg) and serum albumin was maintained; fat mass increased by 7.5 kg (163%) and fat free mass decreased by 6.8 kg (10.6%) from baseline values.

Other studies have evaluated the impact of megestrol acetate on nutritional status in small groups of patients undergoing maintenance dialysis therapy. In one study, 17 elderly HD patients (mean age 68.5 years) with serum albumin < 3.5 gm/dl for 2 months, and deemed at high nutritional risk based on assessment by a renal dietitian, were prescribed megestrol acetate oral suspension (400 mg) twice daily for 6 months (40). Subjective

➡

**Table 1**
Summary of studies on megestrol acetate (MA) in patients undergoing maintenance hemodialysis (HD) and peritoneal dialysis (PD) therapy

| Study population | MA dose | Study duration | Primary outcome | Side effects |
|---|---|---|---|---|
| 24 HD patients (37) | 160 mg/day | 3 months MA; 3 months placebo | No significant increase in serum albumin or lean body mass | None reported |
| 4 HD and 12 PD patients (38) | 20 mg twice daily | 2 – 11 months | Increased serum albumin | None reported |
| 1 HD patient (39) | 320-560 mg/day | 24 weeks | Increased energy and protein intake; increased fat mass | None reported |
| 17 HD patients (40) | 400 mg twice daily | 6 months | Increased dry weight, protein and calorie intake; improved SGA score | Diarrhea, confusion, hyperglycemia, headache, dizziness. |
| 9 HD and 1 PD patient (42) | 400 mg/day | 16 weeks | Increased weight, BMI, body fat, triceps skinfold, serum albumin, protein and calorie intake | No major side effects reported |
| 32 PD patients (43) | 160 mg/day | 23 months | Increased weight and serum albumin | None observed |

global assessment (SGA) and nutrition-related serum chemistries were evaluated monthly, and dry weight was tracked throughout the study. A high incidence of side effects including diarrhea, confusion, hyperglycemia, headaches and dizziness caused some subjects to reduce megestrol acetate dosage or withdraw from the study. In 3 patients completing the entire study, dry weight, protein intake, calorie intake, SGA score and sense of well-being improved. There was no significant change in serum albumin or other laboratory parameters. In addition to the side effects reported by Boccanfuso et al, megestrol acetate therapy has also been linked to adrenal insufficiency, Cushing's syndrome and diabetes (40,41).

In a more recent study, 10 dialysis patients (9 maintenance HD and 1 chronic PD) received 400 mg megestrol acetate solution daily for 16 weeks (42). All subjects had body weight below 85% of ideal body weight or body mass index (BMI) below 20 kg/m$^2$, with recent unintentional weight loss exceeding 5-10% of dry weight or serum albumin below 3.7 gm/dl. These indicators were for 3 consecutive months prior to study commencement. Anthropometry, dual energy X-ray absorptiometry (DEXA), 24-hour diet recall and biochemical measures of nutritional status were performed throughout the study. Weight and BMI increased by 9%, body fat proportion and triceps skinfold by 31% and 40% respectively, and daily protein and calorie intake increased progressively up to 27-42% by the end of the study. Serum albumin increased from 3.0 to 3.3 gm/dl and continued to increase to 3.6 gm/dl 3 months after the study ended. No major side effects were observed.

When 32 PD patients were treated with 160 mg megestrol acetate daily for up to 23 months (mean treatment duration 5.93±5.12 months), appetite improved in more than two-thirds of the patients (43). Weight gain was statistically significant at the third month and there was a non-significant increase in serum albumin. No side effects were observed.

These studies collectively indicate that small doses of megestrol acetate (up to 400 mg/day) may be effective and safe for treating anorexia and improving nutritional status in patients undergoing maintenance dialysis therapy. However, additional placebo-controlled studies with larger patient populations are needed to confirm these findings, and the impact of megestrol acetate on morbidity and mortality rates should also be determined. Megestrol acetate is excreted by the kidney and is not removed by hemodialysis (37), indicating the need for caution when administering the drug to maintenance dialysis patients. Administration of megestrol acetate in doses exceeding 400 mg/day requires careful monitoring of patients for potential adverse effects.

## References


1. Bossola M, Tazza L, Giungi S, Luciani G. Anorexia in hemodialysis patients: An update. *Kidney Int.* 2006;70:417-422.
2. Kalantar-Zadeh K, Balakrishnan VS. The kidney disease wasting: Inflammation, oxidative stress, and diet-gene interaction. *Hemodial Int.* 2006;10:315-325.
3. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: A systematic review. *Adv Chronic Kidney Dis.* 2007;14:82-99.
4. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am J Clin Nutr.* 2004;80:299-307.
5. Aguilera A, Sanchez-Tomero JA, Selgas R. Brain activation in uremic anorexia. *J Ren Nutr.* 2007; 17:57-61.
6. Raimundo P, Ravasco P, Proenca V, Camilo M. Does nutrition play a role in the quality of life of patients under chronic hemodialysis? *Nutr Hosp.* 2006; 21:139-144.
7. Shinaberger CS, Kilpatrick RD, Regidor DL, McAllister CJ, Greenland S, Kopple JD, Kalantar-Zadeh K. Longitudinal associations between dietary protein intake and survival in hemodialysis patients. *Am J Kidney Dis.* 2006;48:37-49.
8. Burrowes JD, Larive B, Chertow GM, Cockram DB, Dwyer JT, Greene T, Kusek JW, Leung J, Rocco MV; Hemodialysis (HEMO) Study Group. Self-reported appetite, hospitalization and death in haemodialysis patients: Findings from the Hemodialysis (HEMO) Study. *Nephrol Dial Transplant.* 2005;20:2765-2774.
9. Burrowes JD, Dalton S, Backstrand J, Levin NW. Patients receiving maintenance hemodialysis with low vs high levels of nutritional risk have decreased morbidity. *J Am Diet Assoc.* 2005;105:563-572.
10. Acchiardo SR, Moore LW, Latour PA. Malnutrition as the main factor in morbidity and mortality of hemodialysis patients. *Kidney Int Suppl.* 1983;16: S199-S203.
11. Wolfson M. Effectiveness of nutrition interventions in the management of malnourished patients treated with maintenance dialysis. *J Ren Nutr.* 1999;9:126-128.
12. Koretz RL. Does nutritional intervention in protein-energy malnutrition improve morbidity or mortality? *J Ren Nutr.* 1999;9:119-121.
13. Kopple JD. Nutritional status as a predictor of morbidity and mortality in maintenance dialysis patients. *ASAIO J.* 1997;43:246-250.
14. Fouque D, Guebre-Egziabher F, Laville M. Advances in anabolic interventions for malnourished dialysis patients. *J Ren Nutr.* 2003;13:161-165.
15. Fouque D, Peng SC, Shamir E, Kopple JD. Recombinant human insulin-like growth factor-1 induces an anabolic response in malnourished CAPD patients. *Kidney Int.* 2000;57:646-654.
16. Jensen PB, Hansen TB, Frystyk J, Ladefoged SD, Pedersen FB, Christiansen JS. Growth hormone, insulin-like growth factors and their binding proteins in adult hemodialysis patients treated with recombinant human growth hormone. *Clin Nephrol.* 1999; 52:103-109.
17. Johansen KL, Painter P, Sakkas GK, Gordon P, Doyle J, Shubert T. Effects of resistance exercise training and nadrolone decanoate on body composition and muscle function among patients who receive hemodialysis: A randomized, controlled trial. *J Am Soc Nephrol.* 2006;17:2307-2314.
18. Navarro JF, Mora C, Macia M, Garcia J. Randomized prospective comparison between erythropoietin and androgens in CAPD patients. *Kidney Int.* 2002; 61:1537-1544.
19. Johansen KL, Mulligan K, Schambelan M. Anabolic effects of nandrolone decanoate in patients receiving dialysis: A randomized controlled trial. *JAMA.* 1999;281:1275-1281.
20. Gokal R, Harty J. Nutrition and peritoneal dialysis. In: Mitch WE, Klahr S, eds. *Handbook of Nutrition and the Kidney.* 3rd ed. Philadelphia, PA: Lippincott-Raven Publishers;1998.

21. Feliu J, Gonzalez-Baron M, Berrocal A, Artal A, Ordonez A, Garrido P, Zamora P, Garcia de Paredes ML, Montero JM. Usefulness of megestrol acetate in cancer cachexia and anorexia. A placebo-controlled study. *Am J Clin Oncol.* 1992;15: 436-440.
22. Loprinzi CL, Ellison NM, Schaid DJ, Krook JE, Athmann LM, Dose AM, Mailliard JA, Johnson PS, Ebbert LP, Geeraerts LH. Controlled trial of megestrol acetate for the treatment of cancer anorexia and cachexia. *J Natl Cancer Inst.* 1990;82:1127-1132.
23. Oster MH, Enders SR, Samuels SJ, Cone LA, Hooton TM, Browder HP, Flynn NM. Megestrol acetate in patients with AIDS and cachexia. *Ann Intern Med.* 1994;121:400-408.
24. Von Roenn JH, Armstrong D, Kotler DP, Cohn DL, Klimas NG, Tchekmedyian NS, Cone L, Brennan PJ, Weitzman SA. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med.* 1994;121:393-399.
25. Yeh SS, Schuster MW. Geriatric cachexia: The role of cytokines. *Am J Clin Nutr.* 1999;70:183-197.
26. Cangiano C, Laviano A, Muscaritoli M, Meguid MM, Cascino A, Rossi Fanelli F. Cancer anorexia: New pathogenic and therapeutic insights. *Nutrition.* 1996;12 (suppl 1):S48-S51.
27. Plata-Salaman CR. Cytokines and feeding suppression: An integrative view from neurologic to molecular levels. *Nutrition.* 1995;11 (suppl 5):674-677.
28. Aguilera A, Selgas R, Codoceo R, Bajo A. Uremic anorexia: A consequence of persistently high brain serotonin levels? The tryptophan/serotonin disorder hypothesis. *Perit Dial Int.* 2000;20:810-816.
29. Alvarez V, Diez JJ, Aguilera A, Selgas R, Codoceo R, Bajo MA. Anorexia in end-stage renal disease: Pathophysiology and treatment. *Expert Opin Pharmacother.* 2001;2:1825-1838.
30. Macdonald C, Rush DN, Bernstein KN, McKenna RM. Production of tumor necrosis factor alpha and hemodialysis. *Nephron.* 1993;65:273-277.
31. Wong CK, Szeto CC, Chan MH, Leung CB, Li PK, Lam CW. Elevation of pro-inflammatory cytokines, C-reactive protein and cardiac troponin T in chronic renal failure patients on dialysis. *Immunol Invest.* 2007;36:47-57.
32. Kapas L, Hong L, Cady AB, Opp MR, Postlethwaite AE, Seyer JM, Krueger JM. Somnogenic, pyrogenic, and anorectic activities of tumor necrosis factor-alpha fragments. *Am J Physiol.* 1992;263:R708-R715.
33. Carrero JJ, Qureshi AR, Axelsson J, Avesani CM, Suliman ME, Kato S, Barany P, Snaedal-Jonsdottir S, Alvestrand A, Heimburger O, Lindholm B, Stenvinkel P. Comparison of nutritional and inflammatory markers in dialysis patients with reduced appetite. *Am J Clin Nutr.* 2007;85:695-701.
34. Karcic E, Philpot C, Morley JE. Treating malnutrition with megestrol acetate: Literature review and review of our experience. *J Nutr Health Aging.* 2002;6:191-200.
35. Yeh SS, Wu SY, Levine DM, Parker TS, Olson JS, Stevens MR, Schuster MW. The correlation of cytokine levels with body weight after megestrol acetate treatment in geriatric patients. *J Gerontol A Biol Sci Med Sci.* 2001;56:M48-M54.
36. Yeh S, Wu SY, Levine DM, Parker TS, Olson JS, Stevens MR, Schuster MW. Quality of life and stimulation of weight gain after treatment with megestrol acetate: Correlation between cytokine levels and nutritional status, appetite in geriatric patients with wasting syndrome. *J Nutr Health Aging.* 2000; 4:246-251.
37. Williams JL, Perius M, Humble A, Sigler D, Urbanes A, Shapiro HS. Effect of megestrol acetate on the nutritional status of malnourished hemodialysis patients [abstract]. *J Ren Nutr.* 1997;7: 231.
38. Lien YH, Ruffenach SJ. Low dose megestrol increases serum albumin in malnourished dialysis patients. *Int J Artif Organs.* 1996;19:147-150.
39. Burrowes JD, Bluestone PA, Wang J, Pierson RN. The effects of moderate doses of megestrol acetate on nutritional status and body composition in a hemodialysis patient. *J Ren Nutr.* 1999;9:89-94.
40. Boccanfuso JA, Hutton M, McAllister B. The effects of megestrol acetate on nutritional parameters in a dialysis population. *J Ren Nutr.* 2000;10:36-43.
41. Mann M, Koller E, Murgo A, Malozoxski S, Bacsanyi J, Leinung M. Glucocorticoidlike activity of megestrol. A summary of Food and Drug Administration experience and a review of the literature. *Arch Intern Med.* 1997; 157:1651-1656
42. Rammohan M, Kalantar-Zadeh K, Liang A, Ghossein C. Megestrol acetate in a moderate dose for the treatment of malnutrition-inflammation complex in maintenance dialysis patients. *J Ren Nutr.* 2005;15:345-355.
43. Costero O, Bajo MA, del Peso G, Gil F, Aguilera A, Ros S, Hevia C, Selgas R. Treatment of anorexia and malnutrition in peritoneal dialysis patients with megestrol acetate. *Adv Perit Dial.* 2004;20:209-212.