TITLE

In patients with End Stage Renal Disease on dialysis, are appetite stimulants an effective means for improving nutrition status?

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TABLE OF CONTENTS

ABSTRACT

Statement of Learning: Determine effectiveness of appetite stimulants in improving nutrition status of dialysis patients with End-Stage Renal Disease (ESRD).

Background: Symptoms associated with ESRD create a significant burden. Anorexia related to ESRD is among the most common symptoms. Previous studies have linked poor appetite to increased mortality rates.

Objective: This research aims to evaluate the current evidence for implementing appetite stimulants to improve nutrition status in ESRD.

Methods: Selected studies met the following criteria: participants were over the age of twenty, receiving dialysis treatment with history of anorexia; study groups had five participants minimum in each arm of study; studies could not be older than 2002. Animal studies and review articles were excluded from search. Seven studies met the criteria. These studies were critically appraised in the areas of relevance and validity. Each study received a class ranking related to the study design. Conclusion of research was scored from one to five describing the evidence for implementing this practice.

Results: Outcomes in stronger study designs noted significant increases in appetite, albumin levels, and protein catabolic rates. Weaker studies found significant changes in weight, appetite, and protein catabolic rates, while other nutrition parameters had varying results.

Conclusion: All studies found significant increases in appetite. The evidence justifying appetite stimulants for improving nutrition status received a score of three, describing the evidence as limited and weak. This score is justified by the study design, rating of the majority of the studies found, and lack of adequate sample sizes.

INTRODUCTION

As the prevalence of End-Stage Renal Disease (ESRD) continues to rise, clinicians are compelled to produce solutions that will provide symptom relief in this population in order to reduce the disease burden on the patient. Anorexia is a symptom commonly experienced in a patient suffering from kidney failure often due to metabolic abnormalities that do not respond to dialysis[1]. As a result of tiredness and loss of appetite, the ESRD population is high risk for malnutrition. Previous studies have indicated that poor appetite correlated with increased mortality rate. Thus, medical professionals including dietitians are looking for ways to preserve nutrition status in this population in order to improve mortality rates as well as quality of life. Additionally, correction of anorexia, malnutrition, and inflammation are important facets of care for the dialysis patient population as it may improve poor clinical outcomes[2]. Anorexia as it relates to malnutrition is the symptom that will be examined in the following study. Specifically, the aim of this research is to evaluate the effectiveness of appetite stimulants in improving nutrition status. Currently, there are no guidelines that outline appropriate usage of appetite stimulants within the ESRD population. This research will look at the most recent studies done on use of an appetite stimulant in ESRD and its effects on nutrition status.

Of the most recent studies exploring the effectiveness of appetite stimulants for improving nutrition status in the ESRD population, the majority of the studies use Megestrol Acetate (MA) as the appetite stimulant used to impact parameters of nutrition status. MA is a synthetic, orally active derivate of progesterone, and may induce appetite via stimulation of neuropeptide Y in the hypothalamus or inhibition of proinflammatory cytokines[1]. Today it is commonly used as an appetite stimulant in cancer patients. Even though it is effective as an appetite stimulant in this population, it increases fat mass predominantly and has a minimal

effect on lean body mass. Megestrol Acetate has been shown to effectively improve appetite and nutritional state in both the AIDS and cancer populations[3-5]. It also works as an anti-inflammatory agent, giving it potential for treatment of malnutrition in dialysis patients[6]. Megestrol Acetate is eliminated via renal excretion. Pharmacokinetics of megestrol acetate has not been evaluated in patients with renal impairment, nor has the dialyzability of megestrol acetate been evaluated. Noted side effects of Megestrol acetate include fluid retention, thrombophlebitis, mild alopecia, vaginal bleeding, hot flushes, and mild nausea. Beneficial effects include increase in appetite and increased sense of well-being. Liver function and blood glucose levels should be monitored periodically[7]. The second class of appetite stimulants examined in this research is growth hormone. This hormone impacts the endocrine system and signals hunger cues directly to the brain. Ghrelin has a direct influence on appetite regulation in contrast to appetite stimulants which act indirectly and can cause a wide range of side effects. Neither treatments have been shown to be effective appetite stimulants for patients with ESRD[7].

The aim of this research was to specifically evaluate how appetite stimulants affect nutrition status in patients with ESRD. Nutrition status is determined by evaluating disease state, history (appetite, chewing and swallowing issues, etc.), current weight, weight loss, pre-albumin and prescribed diet. Markers pertinent to malnutrition diagnosis include history and clinical diagnosis, physical exam/clinical signs, anthropometric data, laboratory data, food/nutrient intake, and functional assessment. Improvements in these markers are what this study will be assessing by analyzing data from seven different studies that assess different parameters of nutrition status.

OVERVIEW TABLE

In patients with ESRD on dialysis, are appetite stimulants an effective means for improving nutrition status?

Author, Year, Study Design, Class Rating	Study Type/ Purpose	Study Populations	Intervention	Outcomes	Conclusion	Limitations
Monfared A et al, 2009 Study Design: Randomized Controlled Clinical Trial Class: A Rating: +	Evaluate effect of MA on serum albumin levels in malnourished dialysis patients.	**Treatment group:** N=11, m/f=5/6, mean age 54.09 ± 4.09, Kt/V was 1.82 ± .06, Weight= 59.45 ± 3.07, BMI = 23.37 ± 1.56 **Control group:** N=11, m/f=8/3, mean age 59.91 ± 3.6, Kt/V 1.6 ± .04, mean weight 55.64 ± 2.7,BMI 21.8 ± 0.87	Patients in experimental group were treated with MA, 40 mg BID for two months.	Serum albumin levels rose (P=.008) in experimental group, while levels in control group declined (P=.201). Protein catabolic rate also increased in experimental group (P<.001), while rate decreased in the control group (P=.08) Improved appetite. No statistically significant weight change.	Megestrol acetate, 40 mg BID increases serum albumin levels in hypoalbuminemic dialysis patients without any complications	Small sample size, short follow-up, lack of medium-term nutrition markers, proinflammatory cytokines, patients' appetites, and body-composition determination could be limitations of this study.

Ashby DR et al, 2009 Study Design: Randomized Crossover Trial Class: A Rating: +	Evaluate nutritional and cardiovascular effects of one week of ghrelin administration.	**Treatment Group:** N = 11, age range: 22-71, nine participants were hemodialysis, three were peritoneal dialysis, months on dialysis: 1-14 months, mean BMI: 24.3kg/m^2	Daily injection of 12 micrograms per kilogram of Ghrelin/Saline solution administered one hour before meal and avoiding periods right before hemodialysis. Intervention groups were switched after a wash-out week.	Energy intake increased in participants taking ghrelin for both study meals (P<0.001) as well as increased daily intake during the week (P=0.04). Cytokines and other nutrition labs that were measured did not change significantly.	Sustained improvement in energy balance in malnourished dialysis was obtained using ghrelin supplementation.	Small sample size, study did not last long enough to evaluate effects on weight gain.
Rammohan M et al, 2005 Study Design: Before-After Study Class: D Rating: Neutral	Determine effectiveness of MA for treatment of malnutrition complex in patients with ESRD who were identified to be	**Treatment Group:** N = 10, age range: 38-83, ESRD Diagnosis: HTN (n=3), DM + HTN (n=3), Post-streptococcal Glomerulonephritis (GN) (n=1), Chronic GN (n=1), Cortical necrosis (n=1), Membranous GN, Systemic lupus erythematosus. One patient was PD and the rest were HD.	Patients were instructed to take 400 mg MA solution every day for 16 weeks.	Weight and body mass index increased by 9%, proportion of body fat increased by 31%, and triceps skin fold increased by 40% (P<.01). Serum albumin increased 0.6 g/dL (P=.03).	Admission of megestrol acetate, 400 mg day, may be an effective intervention to correct anorexia, to mitigate inflammation, and improve nutrition state of hypoalbuminemic	Small sample size

	malnourished and at high risk for poor clinical outcome.	Months on dialysis: 4-267		Daily protein and energy intake increased to 42% by the end of the trial (P <or=.01). C-reactive protein declined 0.46 mg/L in eight patients tested without acute infection (P=.06).	dialysis patients	
Kotzmann et al, 2003 Study Design: Before-After Study Class: D Rating: Neutral	Evaluate effect of growth hormone supplemented in malnourished hemodialysis patients.	**Treatment Group:** N = 19, 9M/10F, mean age 59.3 ± 13.4, Etiologies of kidney disease: polycystic kidney disease (n=1), chronic glomerulonephritis (n=10), chronic pyelonephritis (n=4), diabetic and/or hypertensive nephropathy and nephroangiosclerosis (n=4), CVD history (n=10), mean weight: 60.5 ± 12kg	rhGH 0.125IU/kg three times a week for the first four weeks and 0.25 IU/kg three times a week for the remainder of the study.	Serum albumin, prealbumin, transferrin, cholesterol, HDL, cholinesterase as well as predialytic creatinine and blood urea nitrogen showed no significant changes. Total body fat decreased significantly from 17% to 16% (P<0.05). Lean body mass remained stable throughout entire study. CRP levels did not correlate with nutritional, anthropometric, or immunological parameters.	rhGH increases IGF-I concentrations significantly only in first three months of therapy followed by decline toward baseline values. Phagocytic activity of PMNLs was significantly enhanced for the whole study. Total body fat was significantly reduced by rhGH therapy; other nutritional and anthropometric parameters remained unaffected. Therefore, in severely malnourished	Small sample size, sponsored by drug company

					patients, high doses of rhGH could help overcome GH resistance over a period of 12 months.	
Golebiewska JE et al, 2011 Study Design: Before-After Study Class: D Rating: neutral	Evaluate efficacy and safety of MA in malnourished dialysis patients.	**Treatment Group:** N=32, 18M/14F, Mean Age: 69.97 ± 10.8 years, Time on dialysis: 3.55 ± 35.7 months (range: 3-133 months), Causes of ESRD: diabetic nephropathy (n=9), glomerulonephritis (n=7), hypertensive nephropathy (n=3), interstitial nephritis (n=3), polycystic kidney disease (n=2), other (n=8)	Malnourished patients on dialysis were instructed to take 4ml (160 mg) of MA daily in order to determine effects on nutrition, inflammation, and quality of life.	Over six months weight increased from 63.26 ± 13.04 to 65.58 ± 12.53 ($P<0.01$), and BMI increased 23.5±3.8 to 24.66±4.23 ($P<0.001$). Changes became statistically significant after three months of treatment. Serum albumin increased from 36.46 ± 1.82 to 40.33 ± 2.71 ($P<0.001$). Changes became significant after one month of treatment. All participants reported an increase in appetite which was accompanied by an increase in intake	Megestrol acetate may be effective in reversing poor appetite in dialysis patients.It does not reduce inflammation and does not improve quality of life. There is no evidence Megestrol Acetate caused weight gain, or that better appetite means better survival rates in patients with ESRD.	Lacking control group, small sample size, did not measure change in body composition, lack of a visual analogue scale for appetite assessment compared to actual food intake.
Costero O et al, 2004 Study Design: Before-After Study	Determine effects of MA on appetite and parameters of nutrition	**Treatment Group:** N = 32 (intention to treat), Mean age: 64.1±13.8, Mean dialysis duration: 3.93±3.25, Mean Weekly Kt/V: 2.14±0.56, Mean weight: 66.5±6.4 kg, Causes of	PD patients with anorexia and malnutrition (n=32) received 160	Appetite increased in 68.8% of patients. Weight gain became statistically significant after three months of treatment (weight at	MA dosed at 160 mg per day significantly increases appetite and weight gain, increases serum albumin non-	Study did not address method for assessing change in appetite, or record

Class: D Rating: Neutral	while assessing effective dosage and side effects in patients on peritoneal dialysis (PD) for end stage renal disease (ESRD).	ESRD: Diabetes (n=9), Glomerulonephritis (n=5), Nephrosclerosis (n=5), Unknown (n=5), Interstitial Nephritis (n=3), Systemic Lupus Erythematosus (n=2), Polycystic Kidney Disease (n=2), Vasculitis (n=1)	mg of MA per day for a time period ranging from 1-23 months (5.93±5.12 months on average).	third month: 68±10.4 kg; p<.05). Increase in serum albumin was not statistically significant. Protein Catabolic Rate significantly increased after three months of treatment (initial: 0.95±0.32 g/kg/day; third month: 1.13±0.45 g/kg/day; p=0.032).	significantly, and produces no side effects.	compliance when taking MA. Discussion did not review possibility for confounding variables.
Lucas MF et al, 2010 Study Design: Before-After Study Class: D Rating: Neutral	Determine effectiveness of MA as a treatment for anorexia in dialysis patients.	**Treatment Group:** N = 16, Age range: 40-82, Months on HD: 1-163, Mean weight: 58.9±10.8 kg, Cause of anorexia: None (n=9), gastric ulcer with edema (n=1), heminephrectomy and sepsis (n=1), treatment with interferon (n=1), graft intolerance transplantectomy (n=1), HIV (n=1), surgery for cerebral hematoma (n=1), infection of fistula (n=1). Weight loss in two month period before treatment: 0-9 kg Three patients were noted to have diabetes and eight were noted to have a failed kidney transplant.	160 mg MA daily, single dose	Appetite reportedly increased in 81% of participants. Increases in weight, serum albumin, creatinine, and protein catabolic rate were considered to be statistically significant (P-values: <.01, <.05, <.01, <.001 respectively).	MA stimulates appetite in patients on hemodialysis, this stimulation has a positive effect on weight gain and nutrition related labs. Side effects such as hyperglycemia and inhibition of ACTH should be monitored.	Small sample size

SUMMARY OF EVIDENCE

Patient population was composed of patients with ESRD receiving either hemodialysis (HD) or peritoneal dialysis (PD). All patients were considered to be in the adult population with all participants being over the age of 20. Patients had varying etiologies of kidney disease and length of time on dialysis. Appetite increase, weight increase, and increase in protein catabolic rate were all statistically significant. Statistical significance did not become apparent until about 3 months after treatment with MA and one month after treatment with growth hormone. The following will provide a briefing of each of the studies that were evaluated, comparisons between the methodological processes, and identification of commonalities in the outcomes of the studies. Studies are grouped according to strength of study design.

In a randomized controlled clinical trial in 2009, Monfared found that a dosage of 40 mg MA twice a day over the course of two months increased serum albumin levels in hypoalbuminemic dialysis patients without any complications. During the two month study serum albumin levels of participants rose ($P=0.008$) and protein catabolic rates increased ($P<.001$) when compared to the control group. Participants in treatment group all reported increased appetite but statically significant weight change was not achieved during this two month trial[8].

Ashby in 2009 conducted a double-blinded randomized crossover study of a week-long treatment with daily injections of ghrelin in a group of twelve malnourished dialysis patients. Ghrelin treatment immediately and significantly increased appetite evidenced by increased energy intake, and also exhibited long term effectiveness via food diaries kept throughout the week. Participant's response to ghrelin treatment did not diminish after multiple daily injections.

Limitations include that sample size was small and the study duration was not long enough to demonstrate significant changes in nutritional status such as increased body weight. This study concluded that sustained improvement in energy balance in malnourished dialysis patients could be achieved using ghrelin[9].

Kotzmann in 2003 conducted a study that began as a randomized, double-blind, placebo-controlled study and then switched to a before-after study due to a high dropout rate for reasons not associated with study. The purpose of the study was to determine the effects of twelve months of rhGH therapy on polymorphonuclear leukocyte (PMNL) function as well as on nutritional and anthropometric parameters. Nineteen malnourished hemodialysis patients received 0.125 IU/kg three times per week for four weeks and then 0.25 IU/kg three times per week for the remainder of the year. Serum albumin, prealbumin, transferrin, cholesterol, HDL, cholinesterase as well as predialytic creatinine and blood urea nitrogen showed no significant changes. Total body fat decreased significantly from 17% to 16% ($P<0.05$). Lean body mass remained stable throughout entire study. The application of this treatment is limited due to the small sample size[10].

Golebiewska (2011) implemented a before-after study that found that MA dosed at 160 mg per day up to six months in malnourished dialysis patients increased appetite in all participants, significantly increased weight, BMI, Subjective Global Assessment Score, and albumin concentration ($P<0.05$). No significant changes in levels of inflammatory markers or quality of life. Side effects included over hydration, excessive weight gain, and hyperglycemia. Researchers concluded MA may be effective in improving appetite in carefully selected maintenance dialysis patients. Use should be monitored due to potential side effects[11].

Rammohan (2005) found that MA administered at 400 mg per day may have some benefit for correcting anorexia, decreasing inflammation, and improving nutrition status in hypoalbuminemic dialysis patients. Participants must have been identified to be malnourished and at high risk for poor clinical outcome. Participants in this study had various etiologies of kidney disease and the majority of the participants received hemodialysis. Treatment length lasted for sixteen weeks. Appetite stimulant improved weight and BMI by nine percent, and proportion of body fat increased by thirty-one percent. Triceps skin fold increased by forty percent ($P<.01$). Serum albumin increased 0.6 g/dL ($P=.03$). Daily protein and energy intake increased to forty-two percent by the end of the trial ($P\leq.01$). Fat free mass decreased ($P=.001$), body fat increased ($P=.001$), and fat weight increased ($P=.002$). This study was a before-after study and was limited by its small sample size[12].

Costero conducted a before-after study in 2004 that set out to determine the effects of MA on appetite and on parameters of nutrition while assessing effective dosage and side effects. This study was only done in patients receiving PD. Participants received 160 mg of MA daily. The mean duration of MA treatment was 5.93 ± 5.12 months. Weight gain did not become statistically significant until three months of treatment was accomplished. Increase in serum albumin was not significant. Protein catabolic rate increased significantly after the third month of treatment. Appetite improved in sixty-eight percent of participants. There were not observed side effects of MA at this dose. These results are limited by the small sample size used in this study[13].

Lucas in 2010 conducted a before-after study that attempted to determine the effectiveness of MA as a treatment for anorexia in dialysis patients. Sixteen patients were treated with 160 mg/day of MA as a single dose. Significant increase in dry weight, albumin and creatinine, and protein catabolism rate were observed after three months of treatment. Thirteen of

participants experienced an increase in appetite. Some participants experienced an increase in blood glucose. Researchers concluded that MA stimulates appetite in patients on hemodialysis who report anorexia. Increased weight accompanies appetite increase. Study is limited by small sample size[14].

Methodological Statements

The strongest studies in terms of research design, and had a positive rating in validity and relevance were Monfared and Ashby. The study done by Monfared was a randomized controlled clinical trial. Participants were recruited from a dialysis center and had to have serum albumin levels less than 3.5 g/dL for at least two months. Eighteen participants enlisted in the study. Patients' ages ranged from 50 to 62 years. All participants in this study were receiving hemodialysis. Researchers administered 40 mg of MA to participants twice a day for a period of two months to the treatment group and a placebo to the control group. Serum albumin and protein catabolic rate were measured at baseline and again at the end of the study. Researchers were blinded when analyzing raw data[8].

In the study done by Ashby, nutritional and cardiovascular effects of ghrelin administration were evaluated in a randomized double-blinded crossover design. Twelve participants were recruited from a large renal center in the UK, ages ranged from 22-71 years, nine received HD and three received PD, patients in study had been receiving dialysis from 1-14 months. Mean BMI of participants was 24.3 kg/m^2. All participants had to have two markers of malnutrition in order to be included in the study. Energy intake was measured at study meal day one after ghrelin/placebo injections and study meal day 8 before ghrelin/placebo injections. Ghrelin and acyl ghrelin levels in plasma were measured at time of injection, 30 minutes later

subjects began to eat their meal and the levels were checked a second time, and levels were re-checked 30 minutes after meal began. Participants recorded daily intake in food diaries. Glucose and insulin were also measured 30 minutes before mealtime, at mealtime, and 30 minutes from start of meal. Intervention groups were switched after one wash-out week[9].

The remainders of the studies evaluated were before-after studies with neutral validity ratings. Golebiewska, Costero, and Lucas tested the effectiveness of MA for improving markers of malnutrition including appetite, BMI, and albumin. These studies prescribed one daily dose of 160 mg MA to participants for a minimum of one month and a maximum of twenty-three months. The average length of treatment was four months. In the study by Rammohan the intensity of the intervention was increased. Participants were malnourished dialysis patients at high risk for poor clinical outcomes. Patients were prescribed daily doses of 400 mg of MA over a period of four months. All results were limited as a result of small sample sizes[11-13].

One remaining study was also a before-after study with a neutral validity rating. Kotzmann evaluated the effect of growth hormone supplementation in malnourished hemodialysis patients. Researchers administered rhGH at 0.125 IU/kg three times a week for four weeks and 0.25 IU/kg three times a week for the remainder of the year. Serum albumin, prealbumin, total body fat and lean body mass was recorded in this study. This study was the only study sponsored by a drug company. The results of this study were also limited by small sample size[10].

Outcome Impact Statements

All studies reported significant increases in different parameters of nutrition status. Monfared, Golebiewska, Rammohan, and Lucas reported significant increases in serum albumin.

Kotzman and Costero reported that there were no significant changes in serum albumin. In Kotzman's study, this may be attributed to the use of rhGH as an appetite stimulant. Variance of results found in Costero's study may be due to the fact that one hundred percent of participants were on PD. Monfared and Costero reported significant increases in protein catabolic rates. Monfared, Golebiewska, Costero, and Lucas reported significant increase in appetite. Golebiewska, Rammohan, Costero, and Lucas reported significant increases in weight. Monfared reported that weight change was not statistically significant. This could be a reflection of the daily dosage of MA and the length of the study. In this study, the intervention was 40 mg of MA twice a day for two months. The other studies evaluating the effects of MA dosed at least 160 mg per day and reported that weight change did not become statistically significant until three months of treatment was reached. Rammohan and Golebiewska reported significant increases in BMI. Golebiewska, Rammohan, and Ashby reported significant increases in energy intake. Additionally, the study by Kotzmann found that with rhGH treatment total body fat decreased and lean body mass remained stable throughout the study[8-14].

In summary, the strongest study designs with positive validity ratings found that appetite stimulants improve serum albumin levels, increase protein catabolic rate, improve appetite, and increase energy intake. Monfared reported no significant changes in weight over the two month period. The second group of studies was before-after designs and was given a neutral rating. These studies reported significant changes in weight gain, BMI, appetite, energy intake, and protein catabolic rate in response to an appetite stimulant. In the majority of the studies using MA as the intervention, significant results were not seen until three months of treatment had been reached. Ghrelin therapy, as demonstrated by Ashby, produced significant results after one

week of treatment. Study did not last long enough to evaluate effect on weight, but there was significant increase in energy intake and appetite[8-14].

CONCLUSION

The evidence gathered from the studies discussed in this research conclude that all appetite stimulants in these studies are an effective means for improving certain parameters contributing to nutrition status of a patient with ESRD, including improved serum albumin levels, increased protein catabolic rate, improved appetite, increased energy intake, and weight gain. Of the current studies available for review, small sample size and inadequate study design are the largest limitations when it comes to justification for applying the findings of these studies into clinical practice without reservation. Due to these limitations the grade assigned to this question is Grade III: Limited. More studies with stronger research designs and larger sample sizes should be conducted over an adequate amount of time in order to determine if a higher grade can be assigned. Because many appetite stimulants are excreted in the urine, more studies should be done to evaluate the severity of the side effects in patients with kidney disease, as well as to better determine an effective dose for patients with ESRD. Additionally, more research is needed to better determine the weight gain attributed to fat mass versus lean body mass in order to gain deeper insight into the cause for weight gain and if it will really be beneficial for cachectic renal patients who have a greater need for increased lean body mass rather than fat mass.

When prescribing appetite stimulants in patients with ESRD for the purpose of improving nutrition status, care-givers should monitor side-effects, especially signs of fluid retention and hyperglycemia to ensure patient safety. Significant improvements in nutrition status should not be expected until three months of treatment when using MA. Application of findings should be limited to the adult population. Studies involving children have yet to be evaluated.

REFERENCES

1. Carrero JJ, Aguilera A, Stenvinkel P, et al: Appetite disorders in uremia. *J Ren Nutr*. 2008; 18:107-113.

2. Koretz RL: Does Nutritional Intervention in Protein-energy Malnutrition Improve Morbidity or Mortality? *J Ren Nutr.* 1999; 9:119-121.

3. Mann M, Koller E, Murgo A, et al. 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.

4. 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.

5. Yeh S, Wu SY, Levine DM, et al. 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.

6. Mantovani G, Maccio A, Lai P, et al. Cytokine Activity in Cancer-related Anorexia/Cachexia: Role of Megestrol Acetate and Medroxyprogestrerone Acetate. *Semin Oncol*. 1998; 25:45-52.

7. Femia RA, Goyette R, Richert E. the Science of Megestrol Acetate Delivery: Potential to Improve Outcomes in Cachexia. *Bio-drugs*. 2005; 19:179-187.

8. Monfared A, Heidarzaldeh A, Ghaffari M, Akbarpour M. Effect of Megestrol Acetate on Serum Albumin Level in Malnourished Dialysis Patients. J of Renal Nutrition. 2009; 19 (2): 167-171.

9. Ashby DR, Ford HE, Wynne KJ, Wren AM, Murphy KG, Busbridge M, Brown EA, Taube DH, Ghatei MA, Tam FWK, Bloom SR, Choi P. Sustained Appetite Improvement in Malnourished Dialysis Patients by Daily Ghrelin Treatment. *Kidney International.*2009; 76: 199-206.

10. Kotzmann H, Schmidt A, Lercher P, Schuster E, Geyer G, Frisch H, Horl WH, Mayer G, Luger A. One-Year Growth Hormone Therapy Improves Granulocyte Function Without Major Effects on Nutritional and Anthropometric Parameters in Malnourished Hemodialysis Patients. *Nephron Clin Pract*. 2003; 93: c75-c82.

11. Golebiewska JE, Lichodziejewska-Niemierko M, Aleksandrowicz-Wrona E, Majkowicz M, Lysiak-Szydlowska W, Rutkowski B. Influence of Megestrol Acetate on Nutrition, Inflammation and Quality of Life in Dialysis Patients. *Int Urol Nephrol.* 2011; 44: 1211-1222.

12. Rammohan M, Kalantar-Zadeh K, Liang A, Ghossin C. Megestrol Acetate in a Moderate Dose for the Treatment of Malnutrition-Inflammation Complex in Maintenance Dialysis Patients. *J of Renal Nutrition*. 2005; 15 (3): 345-355.

13. Costero O, Bajo MA, Peso GD, Gil F, Aguilera A, Ros S, Hevia C, Selgas R. Treatment of Anorexia and Malnutrition in Peritoneal Dialysis Patients with Megestrol Acetate. *Advances in Peritioneal Dialysis.* 2004; 20:209-212.

14. Lucas MF, Teruel JL, Burguera B, Sosa H, Rivera M, Palomares JRR, Marcen R, Quereda C. Treatment of Uraemic Anorexia with Megestrol Acetate. Spanish Nephrology Society. 2010; 30 (6): 646-652.

Table 2.0 Search Plan and Results Question
In patients with ESRD on dialysis, are appetite stimulants an effective means for improving nutrition status?

Date of Literature Review for the Evidence Analysis
November 2014

Inclusion Criteria
- **Age:** Adults >20y
- **Setting:** Any
- **Health Status:** Any + ESRD with Anorexia + Dialysis
- **Nutrition Related Problem/Condition:** malnourished
- **Size of Study Groups:** The sample size must equal 5 individuals for each study group. For example, this would include 5 patients in the intervention group and 5 patients in the control or comparison group.
- **Year Range:** >2002
- **Language:** Limited to articles published in English.

Exclusion Criteria
- **Age:** Young adults less than 30 years of age, infants, children, and adolescents.
- **Health Status:** Pre-dialysis
- **Nutrition Related Problem/Condition:** adequately nourished
- **Study Design:** Animal studies, review articles
- **Size of Study Groups:** less than 5 individuals in each arm of study
- **Year Range:** <2002
- **Language:** Articles not in English.

mESH terms (inclusion): kidney failure, chronic/therapy; Human Growth Hormone/administration and dosage; ESRD; appetite; nutrition; renal dialysis; megestrol acetate; nutrition status; appetite stimulant/drug therapy; appetite stimulants; dialysis

Search Terms: Search Vocabulary

Health Condition: ESRD, chronic kidney failure, renal dialysis, malnutrition

Intervention: appetite stimulant, Human Growth Hormone, megestrol acetate, nutrition

Type of Study Design: Clinical Studies, RCTs, Cohort and Case-Control Studies

Electronic Databases

Database: Pubmed

Filters: Clinical trials, human subjects

Search Terms: kidney failure, chronic/therapy; human growth hormone; administration and dosage

Hits: 14

Articles to review: 1

Total articles identified to review from electronic database: 3

List of Articles Included from Electronic Database

Kotzmann H, Schmidt A, Lercher P, Schuster E, Geyer G, Frisch H, Horl WH, Mayer G, Luger A. One-Year Growth Hormone Therapy Improves Granulocyte Function Without Major Effects on Nutritional and Anthropometric Parameters in Malnourished Hemodialysis Patients. *Nephron Clin Pract*. 2003; 93: c75-c82.

List of Excluded Articles with Reason:

Article	Reason for exclusion
Fouque D, Peng SC, Shamir E, Kopple JD. Recombinant Human Insulin-like Growth Factor-1 Induces an Anabolic Response in Malnourished CAPD Patients. *Kidney International.* 2000; 57: 646-654.	3 subjects in each arm of study

***11 remaining hits excluded based upon title.**

Database: Pubmed

Filters: Clinical trials, human subjects

Search Terms: ESRD, appetite, nutrition

Hits: 18

Articles to review: 3

Total articles identified to review from electronic database: 4

List of Articles Included from Electronic Database

Rammohan M, Kalantar-Zadeh K, Liang A, Ghossin C. Megestrol Acetate in a Moderate Dose for the Treatment of Malnutrition-Inflammation Complex in Maintenance Dialysis Patients. *J of Renal Nutrition*. 2005; 15 (3): 345-355.

Golebiewska JE, Lichodziejewska-Niemierko M, Aleksandrowicz-Wrona E, Majkowicz M, Lysiak-Szydlowska W, Rutkowski B. Influence of Megestrol Acetate on Nutrition, Inflammation and Quality of Life in Dialysis Patients. *Int Urol Nephrol.* 2011; 44: 1211-1222.

Monfared A, Heidarzaldeh A, Ghaffari M, Akbarpour M. Effect of Megestrol Acetate on Serum Albumin Level in Malnourished Dialysis Patients. *J of Renal Nutrition.* 2009; 19 (2): 167-171.

List of Excluded Articles with Reason:

Article	Reason for exclusion
Lien YH, Ruffenach SJ. Low Dose Megestrol Increases Serum Albumin in Malnourished Dialysis Patients. *Int J Artif Organs*. 1996; 19 (3):147-150.	Publication date

***14 remaining hits excluded based upon title.**

Database: Pubmed

Filters: Clinical trials, human subjects

Search Terms: appetite stimulant/drug therapy, renal dialysis

Hits: 7

Articles to review: 1

Total articles identified to review from electronic database: 2

List of Articles Included from Electronic Database

Costero O, Bajo MA, Peso GD, Gil F, Aguilera A, Ros S, Hevia C, Selgas R. Treatment of Anorexia and Malnutrition in Peritoneal Dialysis Patients with Megestrol Acetate. *Advances in Peritioneal Dialysis.* 2004; 20:209-212.

List of Excluded Articles with Reason:

Article	Reason for exclusion
Yeh S, Marandi M, Thode HC, Levine DM, Parker T, Dixon T Schuster MW. Report of a Pilot, Double-Blind, Placebo-Controlled Study of Megestrol Acetate in Elderly Dialysis Patients With Cachexia. *J of Renal Nutrition.* 2010; 20 (1): 52-62	Small sample size. 6 subjects completed study.
Wynne K, Giannitsopoulou K, Small CJ, Patterson M, Frost G, Ghatei MA, Brown EA, Bloom SR, Choi P. Subcutaneous Ghrelin Enhances Acute Food Intake in Malnourished Patients Who Receive Maintenance Peritoneal Dialysis: A Randomized, Placebo-Controlled Trial. *J Am Soc Nephrol.*2005; 16: 2111-2118.	Small sample size. 9 subjects total.

***5 remaining hits excluded based upon title.**

Database: Pubmed

Filters: Clinical trials, human subjects

Search Terms: ghrelin, dialysis, appetite

Hits: 4

Articles to review: 1

Total articles identified to review from electronic database: 1

List of Articles Included from Electronic Database

Ashby DR, Ford HE, Wynne KJ, Wren AM, Murphy KG, Busbridge M, Brown EA, Taube DH, Ghatei MA, Tam FWK, Bloom SR, Choi P. Sustained Appetite Improvement in Malnourished Dialysis Patients by Daily Ghrelin Treatment. *Kidney International.*2009; 76: 199-206.

***3 remaining hits excluded based upon title.**

Database: Pubmed

Filters: human subjects

Search Terms: megestrol acetate/therapeutic use, renal dialysis, nutritional status

Hits: 5

Articles to review: 0

Total articles identified to review from electronic database: 2

List of Excluded Articles with Reason:

Article	Reason for exclusion
Boccanfuso JA, Hutton M, McAllister B. The Effects of Megestrol Acetate on Nutritional Parameters in a Dialysis Population. *J of Renal Nutrition.* 2000; 10 (1): 36-43.	Publication date
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 (2):89-94.	Publication date

***3 remaining hits excluded based upon title.**

Database: Ebsco Host: Medline Complete

Filters: Full text, publication date: 2003-2014, abstract available, human subjects, Major headings: megestrol acetate, anorexia, kidney failure, chronic

Search Terms: uremic anorexia, megestrol acetate, renal dialysis

Hits: 4

Articles to review: 1

Total articles identified to review from electronic databases: 1

List of Articles Included from Electronic Databases

Lucas MF, Teruel JL, Burguera B, Sosa H, Rivera M, Palomares JRR, Marcen R, Quereda C. Treatment of Uraemic Anorexia with Megestrol Acetate. *Spanish Nephrology Society.* 2010; 30 (6): 646-652.

***3 remaining hits excluded based upon title.**

Summary of Articles Identified to Review

Number of Primary Articles Identified: 7

Number of Review Articles Identified: 0

Total Number of Articles Identified: 7

Number of Articles Reviewed but Excluded: 6

Academy of Nutrition and Dietetics
Evidence Analysis Library® Worksheet Template and
Quality Criteria Checklist: Primary Research

Citation	Monfared A, Heidarzaldeh A, Ghaffari M, Akbarpour M. Effect of Megestrol Acetate on Serum Albumin Level in Malnourished Dialysis Patients. J of Renal Nutrition. 2009; 19 (2): 167-171.
Study Design	Randomized Controlled Trial
Class	A
Quality Rating	☒ + (Positive) ☐ - (Negative) ☐ ⊘ (Neutral)
Research Purpose	Evaluate effect of megestrol acetate on serum albumin levels in malnourished dialysis patients.
Inclusion Criteria	Serum albumin level of less than 3.5 g/dL for at least 2 months, at least 3 months on dialysis treatment, effective hemodialysis, normal hepatic function, and C-reactive proteinlevel less than 0.8 mg/dL.
Exclusion Criteria	Malignancy or active autoimmune disease, diabetes mellitus with debilitating end-organ damage, deep anemia and decompensated congestive heart failure, patients on corticosteroid therapy, patients with symptoms of inflammatory or infectious disease during study.
Description of Study Protocol	Recruitment: Patients were recruited from a dialysis center at Razi Hospital in Rasht, Iran. Patients were randomly assigned to experimental and control groups. Design: Randomized Controlled Clinical Trial Blinding used (if applicable): Researchers were blinded when analyzing the raw data before they knew if the data belonged to the control or intervention group. Intervention (if applicable): Patients in experimental group were treated with megestrol acetate, 40 mg BID for two months. Statistical Analysis: Comparison of serum albumin levels was determined by using a paired t-test. Differences between experimental and control groups were analyzed using a repeated nonparametric standard test with Wilcoxon signed rank. Kolmongorov-Smirnov (KS) one-sample tests were used to evaluate assigned albumin values in each pair and in both groups. P<.05 was considerd statistically significant.
Data Collection Summary	Timing of Measurements: In both groups serum albumin level and protein catabolic rate were measured at baseline and again after two months. Dependent Variables: Serum albumin and protein catabolic rate

	Independent Variables: Megestrol acetate, 40 mg BID for two months. Control Variables: Serum albumin levels were measured using the colorimetric method with an Alcyon 33, using the bromocresol green method. Protein catabolic rate was calculated using a standardized formula.
Description of Actual Data Sample	Initial: 22 (13 Males 9 Females) Attrition (final N): 18 Age: 54.09+/-4.09 in experimental; 59.91+/-3.6 in control Ethnicity: Not described Other relevant demographics: All patients were hemodialysis patients, Kt/V was 1.82+/-.06 in experimental group and 1.6+/-.04 in control group. One participant in the experimental group died, and two participants in the control group died. Anthropometrics: Average weight for experimental group was 59.45+/-3.07 and 55.64+/-2.7 in control group. Average BMI was 23.37+/-1.56 in experimental group and 21.8+/-.87 in control group. Location: Dialysis center at Razi Hospital in Rasht, Iran.
Summary of Results	Key Findings: After 2 months of treatment, serum albumin levels in experimental group rose 3.31+/-.31 g/dL to 4.41+/-0.31 g/dL (P=.008), while levels in control group declined from3.35+/-0.21 to 3.02+/-0.48 g/dL (P=.201). Difference between groups was considered to be significant (P=.002). Protein catabolic rate also increased in experimental group from 0.87+/-0.05 to 1+/-0.04 (P<.001), while rate decreased in the control group from 0.87+/-0.03 to 0.85+/-0.02 (P=.08). Other Findings: There was no significant changes in total weight of patients from pretreatment to posttreatment (P>.05), but almost all patients in experimental group reported an improved appetite.
Author Conclusion	Megestrol acetate, 40 mg BID increases serum albumin levels in hypoalbuminemic dialysis patients without any complications.
Reviewer Comments	*Number of cases, short followup, lack of medium-term nutrition markers, proinflammatory cytokines, patients' appetites, and body-composition determination could be limitations of this study.*
Funding Source	Not described.

Quality Criteria Checklist: Primary Research

Symbols Used	*Explanation*
+	***Positive** – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	***Negative** – Indicates that these issues have not been adequately addressed.*
⊘	***Neutral** – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
4. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
1. Was the <u>research question</u> clearly stated?	1	Yes
1.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
1.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
1.3. Were the target population and setting specified?	1.3	Yes
2. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
2.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
2.2. Were criteria applied equally to all study groups?	2.2	Yes
2.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
2.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
3. Were <u>study groups comparable</u>?	3	Yes
3.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
3.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Yes
3.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
3.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	N/A
3.5. If case control study, were potential confounding factors comparable for cases		

and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
3.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A

4. Was method of handling <u>withdrawals</u> described?	4	Yes
4.1. Were follow up methods described and the same for all groups?	4.1	Yes
4.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
4.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
4.4. Were reasons for withdrawals similar across groups	4.4	Yes
4.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
5. Was <u>blinding</u> used to prevent introduction of bias?	5	N/A
5.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
5.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
5.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	N/A
5.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
5.5. In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
6. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
6.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
6.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	Yes
6.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
6.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
6.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	N/A
6.6. Were extra or unplanned treatments described?	6.6	N/A
6.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Yes
6.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
7. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
7.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
7.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
7.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
7.4. Were the observations and measurements based on standard, valid, and	7.4	Yes

reliable data collection instruments/tests/procedures?	7.5	Yes
7.5. Was the measurement of effect at an appropriate level of precision?	7.6	Yes
7.6. Were other factors accounted for (measured) that could affect outcomes?	7.7	Yes
7.7. Were the measurements conducted consistently across groups?		

8. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
8.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
8.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
8.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
8.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	N/A
8.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	No
8.6. Was clinical significance as well as statistical significance reported?	8.6	No
8.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
9. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
9.1. Is there a discussion of findings?	9.1	Yes
9.2. Are biases and study limitations identified and discussed?	9.2	Yes
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Unclear
10.1. Were sources of funding and investigators' affiliations described?	10.1	No
10.2. Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)

If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (∅)

If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)

If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Academy of Nutrition and Dietetics
Evidence Analysis Library® Worksheet Template and
Quality Criteria Checklist: Primary Research

Citation	Golebiewska JE, Lichodziejewska-Niemierko M, Aleksandrowicz-Wrona E, Majkowicz M, Lysiak-Szydlowska W, Rutkowski B. Influence of Megestrol Acetate on Nutrition, Inflammation and Quality of Life in Dialysis Patients. Int Urol Nephrol. 2011; 44: 1211-1222.
Study Design	Before-After Study
Class	D
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	Evaluate efficacy and safety of megestrol acetate in malnourished dialysis patients.
Inclusion Criteria	Minium 3 months treatment with maintenance dialysis treatment Serum albumin concentration <= 3.8
Exclusion Criteria	Concurrent use of glucocorticoids Inadequate dialysis defined by a Kt/V of <1.2 for MDH and <2.0 for CPD patients
Description of Study Protocol	Recruitment: Recruited and screened MHD and CPD patients from six different hemodialysis centres and two peritoneal dialysis centres. Design: Multicenter prospective design. Blinding used (if applicable): N/A Intervention (if applicable): Malnourished patients on dialysis were instructed to take 4ml (160 mg) of megestrol acetate daily in order to determine effects on nutrition, inflammation, and quality of life. Statistical Analysis: Kolmogorow-Smirnow and Lilliefors tests were used to assess normalcy of the distributions. Fisher's F test and Levene's test were used to assess the equality of variance. The Spearman's or Pearson's rank order were used to explore relationship between indicies at baseline. Parametric or Frieman's ANOVA were used to assess significance of changes for the repeated measures. Post hoc analyses were the Least Significant Differences test and Conover test.
Data Collection Summary	Timing of Measurements: Weight, BMI, and nutrition related labs were collected every month for six months following baseline measurement. SGA and quality of life questionnaires were collected every three months after baseline measurement. Dependent Variables: Weight, BMI, serum albumin, triglycerides, total

	cholesterol, hsCRP, cytokines (IL-1 beta and IL-6), dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, subcutaneous fat, signs of muscle wasting, and quality of life. Independent Variables: Daily dosage of 4 ml Megestrol Acetate solution (160 mg). Control Variables: Hemodialysis patients brought in bottles of megestrol acetate for weighing and were wittnessed taking the drug to ensure compliance. They took the drug home on remaining days. Peritoneal dialysis patients brought bottles in for weighing and were asked to return empty bottles. Blood samples were drawn from a peripheral vein in PD patients and from the artero-venous fistula in HD patients before dialysis. Serum was seperated <30 minutes after drawing and stored at -70 degrees C until analysis. Serum albumin, triglycerides and total cholesterol were analyzed using standard lab techniques. Cytokines and hsCRP concentrations were analyzed using by an ELISA kit. The Subjective Global Assessment was used to score participants in the areas of weight change, dietary intake, gastrointestinal symptoms, functional capacity, comorbidity, subcutaneous fat and signs of muscle wasting. Patients were scored from 1 to 7, 7 being well nourished and 1 being malnourished. The Hospital Anxiety and Depression Scale was used to assess level of negative emotions. The Purpose in Life Test was used to assess the intensity of positive emotions.Cantril's Ladder was used to measure life satisfaction. The Brief Fatigue inventory was used to evaluate fatigue.
Description of Actual Data Sample	Initial: 32 (18 Males 14 Females) Attrition (final N): 32 Age: 69.97+-10.8 years (range: 38-85) Ethnicity: Not described Other relevant demographics: Time on dialysis: 3.55+/-35.7 months (range: 3-133) Causes of ESRD: diabetic nephropathy (n=9), glomerulonephritis (n=7), hypertensive nephropathy (n=3), interstitial nephritis (n=3), polycystic kidney disease (n=2), other (n=8) Anthropometrics: Patients participating in study had differing BMIs at baseline. The mean was 23.06+/-3.26.

	Location: Multicenter trial in Poland
Summary of Results	Key Findings: Over the course of six months weight increased from 63.26+/-13.04 to 65.58+/-12.53 (P<0.01), and BMI increased 23.5+/-3.8 to 24.66+/-4.23 (P<0.001). These changes became statistically significant after three months of treatment. Serum albumin increased from 36.46+/-1.82 to 40.33+/-2.71 (P<0.001). These changes became significant after one month of treatment. Changes in triglycerides, total cholesterol, hsCRP, and cytokines (IL-1 beta and IL-6) were not considered to be significant. All participants reported an increase in appetite which was accompanied by an increase in intake. There were no significant changes in the quality of life of participants. Other Findings: Common side effects include overhydration causing pulmonary congestion and dyspnoea, excessive weight gain occured in six subjects, one subject with diabetes experienced hyperglycemia, three patients experienced diarrhea, three patients experienced nausea and vomitting, two patients experienced thrombophlebitis .
Author Conclusion	Megestrol acetate may be effective in reversing poor appetite in dialysis patients.It does not reduce inflammation and does not improve quality of life. There is no evidence Megestrol Acetate caused weight gain, or that better appetite means better survival rates in patients with ESRD.
Reviewer Comments	*This article challenged the thought that improved appetite results in better outcomes for patients with ESRD.*
Funding Source	Ministry of Science and Higher Education

Quality Criteria Checklist: Primary Research

Symbols Used	*Explanation*
+	***Positive –*** *Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	***Negative –*** *Indicates that these issues have not been adequately addressed.*
⊘	***Neutral*** *– indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
5. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
6. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
7. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
8. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
11. Was the <u>research question</u> clearly stated?	1	Yes
11.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
11.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
11.3. Were the target population and setting specified?	1.3	Yes
12. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
12.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
12.2. Were criteria applied equally to all study groups?	2.2	Yes
12.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
12.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
13. Were <u>study groups comparable</u>?	3	N/A
13.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	N/A
13.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	N/A
13.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	N/A
13.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	N/A
13.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
13.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A

14. Was method of handling <u>withdrawals</u> described?	4	Yes
14.1. Were follow up methods described and the same for all groups?	4.1	Yes
14.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for	4.2	Yes

each group? (Follow up goal for a strong study is 80%.)	4.3	Yes
14.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.4	Yes
14.4. Were reasons for withdrawals similar across groups	4.5	N/A
14.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?		
15. Was <u>blinding</u> used to prevent introduction of bias?	5	N/A
15.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
15.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
15.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	N/A
15.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
15.5. In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
16. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
16.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
16.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	Yes
16.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
16.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
16.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	N/A
16.6. Were extra or unplanned treatments described?	6.6	Yes
16.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Yes
16.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
17. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
17.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
17.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
17.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
17.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
17.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
17.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
17.7. Were the measurements conducted consistently across groups?	7.7	Yes

18. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
18.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
18.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
18.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
18.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Yes
18.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
18.6. Was clinical significance as well as statistical significance reported?	8.6	No
18.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	No
19. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
19.1. Is there a discussion of findings?	9.1	Yes
19.2. Are biases and study limitations identified and discussed?	9.2	Yes
20. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
20.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
20.2. Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (∅)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Academy of Nutrition and Dietetics
Evidence Analysis Library® Worksheet Template and
Quality Criteria Checklist: Primary Research

Citation	Rammohan M, Kalantar-Zadeh K, Liang A, Ghossin C. Megestrol Acetate in a Moderate Dose for the Treatment of Malnutrition-Inflammation Complex in Maintenance Dialysis Patients. J of Renal Nutrition. 2005; 15 (3): 345-355.
Study Design	Before-After Study
Class	D
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	Determine effectiveness of Megestrol Acetate for treatment of malnutrition complex in patients with ESRD who were identified to be malnourished and at high risk for poor clinical outcome.
Inclusion Criteria	Participants must have been on dialysis for four months prior to treatment, had an actual body weight less than 85% of ideal body weight or a BMI less than 20 plus one of the following criteria: (1)recent unintentional weight loss greater than 5-10% of targeted weight within a 6 month period and not caused as a result of intercurrent illness, or (2) serum albumin less than 3.7g/dL for 3 consecutive months. All participants had to give informed consent to participate in study.
Exclusion Criteria	Patients were excluded from study if they had severe congestive heart failure, untreated deep venous thrombosis, uncontrolled diabetes, chronic liver disease, concurrent use of appetite stimulants, use of TPN in last six months, concurrent use of glucocorticoids, KT/V of <1.2 for hemodialysis and <2.0 for peritoneal dialysis.
Description of Study Protocol	Recruitment: Maintenance hemodialysis and chronic peritoneal dialysis patients from the Renal Care Group Northwestern University Dialysis facility were screened for eligibility criteria and recruited. Design: Prospective , open-label study design was used. Blinding used (if applicable): N/A Intervention (if applicable): Patients were instructed to take 400 mg Megestrol Acetate solution everday for 16 weeks. Statistical Analysis: Values for before and after treatment were compared using a dependent t-test and a nonparametric test to determine significance of results. p<.05 considered to be statistically significant, p-value between .05-.10 were considered to be borderline significant.
Data Collection Summary	Timing of Measurements: Patients were seen every four weeks to take measurments for data collection.

	Dependent Variables: Measurements included Antropometrics: Weight, BMI, body fat percentage, body fat weight, fat free mass percent, fat free mass weight, total body water percent, tricep skin fold, midarm muscle circumference; Laboratory Values: Serum albumin, c-reactive protein, leptin, glucose, total cholesterol Food Intake and Perception of Well Being and Quality of Life were also measured. Independent Variables: Daily dose of 400 mg of Megestrol Acetate solution for 16 weeks. Control Variables: Antropometric Measurements: Heights and weights were measured to the nearest 0.5 cm and 0.1 kg, respectively. Body Composition: DEXA scan was used to measure total body fat and fat free mass. Bioeletrical Body Composition Analyzer Quantum II was used to assess volume status. Biochemical: Serum albumin was measured using bromocresol green.CRP was measured with rate nephelometry using a Beckman Array automated nephelometer. Leptin was measured using ELISA DSL. Intake and Sense of Well Being: One 24-hour recall was obtained during montyly visits, utilizing food models.Nutritionist 4 sortware program was used for nutrient analysis. A modified version of the Kidney Disease and Quality of Life questionnaire was used to evaluate participant's overall sense of well-being. Dialysis Adequacy and Protein Catabolic Rate: Dialysis was evaluated using RCG's protocol which uses the urea kinetic modeling developed by Daugirdas. A simmplified equation using two BUN methods was used to calculate normalized protein nitrogen apperance.
Description of Actual Data Sample	Initial: 16 (4 Males 6 Females) Attrition (final N): 10; 6 participants left: 2 transferred to other dialysis centers, 3 were non-compliant with montylu visit to the GCRC, and one died due to causes unrelated to the study. Age: 38-83 Ethnicity: Not described

	Other relevant demographics: ESRD Diagnosis: HTN (n=3), DM + HTN (n=3), Poststrptococcal Glomerulonephritis (GN) (n=1), Chronic GN (n=1), Cortical necrosis (n=1), Membranous GN, Systemic lupus erythemadosus. One patient was PD and the rest were HD. Months on dialysis: 4, 24, 28, 51, 52, 53, 84, 212, 267 Anthropometrics: Patients' heights, weights, BMI, midarm circumference, midarm muscle circumference, and tricep skin fold were measured. Location: General Clinical Research Center of Northwestern Memorial Hospital in Chicago, IL
Summary of Results	Key Findings: Weight and body mass index increased by nine percent, porportion of body fat increased by 31%, and tricep skin fold increased by 40% (P<.01). Serum albumin increased 0.6 g/dL (P=.03). Serum leptin increaed from 5.2 to 10.7 (P=.09). Daily protein and energy intake increased to 42% by the end of the trial (P <or=.01). C-reactive protein declined 0.46 mg/L in eight patients tested without acute infection (P=.06). FFM increased by 1.4%. Quality of life and appetite was reported to be improved. No major side effects were observed. Other Findings: Weight gain and further improvement in serum albumin continued even three months after trial completion.
Author Conclusion	Admission of megestrol acetate, 400 mg.day, may be an effective intervention to correct anorexia, to mitigate inflammation, and improve nutrition state of hypoalbuminemic dialysis patients.
Reviewer Comments	*To measure patients' preceived quality of life, a modified version of the kidney disease and quality of life questionaire was used.*
Funding Source	Unspecified

Quality Criteria Checklist: Primary Research

Symbols Used	*Explanation*
+	***Positive –*** *Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	***Negative –*** *Indicates that these issues have not been adequately addressed.*
⊘	***Neutral*** *– indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
9. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
10. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
11. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
12. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
21. Was the <u>research question</u> clearly stated?	1	Yes
21.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
21.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
21.3. Were the target population and setting specified?	1.3	Yes
22. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
22.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
22.2. Were criteria applied equally to all study groups?	2.2	Yes
22.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
22.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
23. Were <u>study groups comparable</u>?	3	N/A
23.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	N/A
23.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	N/A
23.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	N/A
23.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	N/A
23.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
23.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A

24. Was method of handling <u>withdrawals</u> described?	4	Yes

24.1. Were follow up methods described and the same for all groups?	4.1	Yes
24.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
24.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
24.4. Were reasons for withdrawals similar across groups	4.4	Yes
24.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
25. Was <u>blinding</u> used to prevent introduction of bias?	5	N/A
25.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
25.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
25.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	N/A
25.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
25.5. In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
26. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	N/A
26.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A
26.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	Yes
26.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
26.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
26.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	N/A
26.6. Were extra or unplanned treatments described?	6.6	N/A
26.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	N/A
26.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
27. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
27.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
27.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
27.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
27.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
27.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
27.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
27.7. Were the measurements conducted consistently across groups?	7.7	Yes

28. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
28.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
28.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
28.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
28.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	No
28.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
28.6. Was clinical significance as well as statistical significance reported?	8.6	No
28.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
29. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
29.1. Is there a discussion of findings?	9.1	Yes
29.2. Are biases and study limitations identified and discussed?	9.2	Yes
30. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Unclear
30.1. Were sources of funding and investigators' affiliations described?	10.1	No
30.2. Was there no apparent conflict of interest?	10.2	Yes
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

Academy of Nutrition and Dietetics
Evidence Analysis Library® Worksheet Template and
Quality Criteria Checklist: Primary Research

Citation	Kotzmann H, Schmidt A, Lercher P, Schuster E, Geyer G, Frisch H, Horl WH, Mayer G, Luger A. One-Year Growth Hormone Therapy Improves Granulocyte Function Without Major Effects on Nutritional and Anthropometric Parameters in Malnourished Hemodialysis Patients. Nephron Clin Pract. 2003; 93: c75-c82.
Study Design	Before-After Study
Class	D
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	Evaluate effect of growth hormone supplementation in malnourished hemodialysis patients.
Inclusion Criteria	Patients had to be on chronic hemodialysis for at least 6 months. Participants additionally had to meet three of the following criteria: serum cholesterol and transferrin levels <200 mg/dL, serum albumin concentrations <41 g, and a body weight <80% of the optimal body weight.
Exclusion Criteria	Not described
Description of Study Protocol	Recruitment: Hemodialysis Clinic Design: Randomized, double-blind, placebo controlled study. Blinding used (if applicable): The study was randomized, double-blind and palcebo controlled (GH/placebo) for the first three months, then switched to an open study for the remaining nine months due to an unexpected high drop out rate. Intervention (if applicable): rhGH 0.125IU/kg three times a week for the first four weeks and 0.25 IU/kg three times a week for the remainder of the study. Statistical Analysis: SAS software, GLM procedure was used to account for unbalanced data, HSD to identify significant deviations in the means of the main effects, general linear model for paired data. Variable were described by their means and standard deviations. Differences where P<0.05 were considered statistically significant.
Data Collection Summary	Timing of Measurements: IGF-I , IGF-BP3, phagocytosis, killing, Glucose uptake of polymorphonuclear leukocytes (PMNLs) basal and PMNLs stimulated, [Ca2+] of PMNLs basal and PMNLs stimulated, lean body mass, and total body fat levels were measured at baseline and every three months for 12 months, except for

	lean body mass and total body fat which were measured at baseline and every three months for the next nine months. Dependent Variables: IGF-I levels, phagocytic activity of PMNLs, and total body fat Independent Variables: Admistration of growth hormone: rhGH 0.125IU/kg three times a week for the first four weeks and 0.25 IU/kg three times a week for the remainder of the study. Control Variables: Preparation of PMNLs and PMNL Function Test: controlled using 10 ml heparinized whole blood Leukocyte-rich plasma was centrifuged at 500g for 25 min at room temperature. PMNLs were harvested and washed twice with Hank's buffered saline with Ca2+ and Mg2+. Viability tested with trypan blue and was always greater than 90%. Blood Tests: Blood was drawn before and after first dialysis of the week and again before the next dialysis for urea determinations used to calculate urea kinetics. Anthropometric Measures: Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg. Body composition was determined by skinfold thickness measurmentusing a Holtain caliper at 11 sites: cheek, chin, pectoral-chest, thoracal-midaxillary, suprailiacal, paraumbilical, subscapular, triceps, front thigh, biceps and popliteal. Skinfolds were measured to the nearest 0.2mm, the mean of three readings was recorded. Total body fat was calculated from Allen and colleagues formula. Total body weight minus total body fat gives lean body mass.
Description of Actual Data Sample	Initial: 19 (9 Males 10 Females) Attrition (final N): 14 Age: 59.3+/-13.4 Ethnicity: Not described Other relevant demographics: Etiologies of kidney disease: polycystic kidney disease (n=1), chronic glomerulonephritis (n=10), chronic pyelonephritis (n=4), diabetic and/or hypertensive nephropathy and nephroangiosclerosis (n=4). Ten patients had a history of CVD. Anthropometrics: Participants were 60.5+/-12kg at the beginning of the study. Location: Not described

Summary of Results	Key Findings: IGF-I: before- 169.2+/-96.5; after- 262.9+/-144.4 ng/ml (P<0.01) IGR-BP3 levels also increased but never reached statistical significance. PMNL phagocytic activity increased significantly (P<0.05) Serum albumin, prealbumin, transferrin, cholesterol, HDL, cholinesterase as well as predialytic creatinine and blood urea nitrogen showed no significant changes. Total body fat decreased significantly from 17% to 16% (P<0.05). Lean body mass remained stable throughout entire study. CRP levels did not correlatewith nutritional, anthropometric, or immunological parameters. Blood glucose rose in two participants who were diabetic. All other patients showed no changes in Hemoglobin A1C or fasting glucose levels. Other Findings: N/A
Author Conclusion	rhGH increases IGF-I concentrations significantly only in first three months of therapy followed by decline toward baseline values. Phagocytic activity of PMNLs was significantly enhanced for the whole study. Total body fat was significantly reduced by rGH thrapy; other nutritional and anthropomentric parameters remained uneffected. Therefore, in severly malnourished patients, high doses of rhGH could help overcome GH resistance over a period of 12 months.
Reviewer Comments	*Study limitations: small sample size; this study did not analyze the effects of this drug on appetite itself. Overall nutrition status is speculated to be improved due to maintenance of lean body mass and loss of total body fat.*
Funding Source	Pharmacia supplied rhGH and placebo preparation.

Quality Criteria Checklist: Primary Research

Symbols Used	*Explanation*
+	***Positive** – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	***Negative** – Indicates that these issues have not been adequately addressed.*
⊘	***Neutral** – indicates that the report is neither exceptionally strong nor exceptionally*

	week

Select a rating from the drop-down menu ↓

Relevance Questions		
13. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
14. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
15. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
16. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
31. Was the <u>research question</u> clearly stated?	1	Yes
31.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
31.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
31.3. Were the target population and setting specified?	1.3	Yes
32. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
32.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
32.2. Were criteria applied equally to all study groups?	2.2	Yes
32.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
32.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
33. Were <u>study groups comparable</u>?	3	Yes
33.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
33.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	Unclear
33.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
33.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Yes
33.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
33.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A

34. Was method of handling <u>withdrawals</u> described?	4	Yes
34.1. Were follow up methods described and the same for all groups?	4.1	Yes
34.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
34.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
34.4. Were reasons for withdrawals similar across groups	4.4	Yes
34.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
35. Was <u>blinding</u> used to prevent introduction of bias?	5	Unclear
35.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	No
35.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
35.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	No
35.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
35.5. In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
36. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
36.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
36.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
36.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
36.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
36.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	Yes
36.6. Were extra or unplanned treatments described?	6.6	Yes
36.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Yes
36.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
37. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
37.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
37.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
37.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
37.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
37.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
37.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
37.7. Were the measurements conducted consistently across groups?	7.7	No

38. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
38.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
38.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
38.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
38.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	No
38.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
38.6. Was clinical significance as well as statistical significance reported?	8.6	No
38.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	No
39. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
39.1. Is there a discussion of findings?	9.1	Yes
39.2. Are biases and study limitations identified and discussed?	9.2	Yes
40. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
40.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
40.2. Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)

If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (∅)

If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)

If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Academy of Nutrition and Dietetics
Evidence Analysis Library® Worksheet Template and
Quality Criteria Checklist: Primary Research

Citation	Ashby DR, Ford HE, Wynne KJ, Wren AM, Murphy KG, Busbridge M, Brown EA, Taube DH, Ghatei MA, Tam FWK, Bloom SR, Choi P. Sustained Appetite Improvement in Malnourished Dialysis Patients by Daily Ghrelin Treatment. Kidney International.2009; 76: 199-206.
Study Design	Randomized Crossover Trial
Class	A
Quality Rating	☒ + (Positive) ☐ - (Negative) ☐ ⊘ (Neutral)
Research Purpose	Evaluate nutrtional and cardiovascular effects of one week of ghrelin administration.
Inclusion Criteria	Age: between 17 and 75 years Patients were clinically well. Patients had to posess at least 2 of the following markers of malnutrition: unintentional weight loss of >5% over the past 6 months; serum albumin <35g/l; untreated cholesterol <4.5 mmol/l; body mass index <20; subjective global assessment score <6; total iron-bining capacity <45%
Exclusion Criteria	No exclusions other that inclusion criteria.
Description of Study Protocol	Recruitment: Eligible patients were identified from hospital records and were invited to participate while getting dialysis or by phone. Patients were recruited from a large renal center in the UK. Design: Randomized double-blinded crossover design Blinding used (if applicable): Participants and researchers were blinded to which participants received ghrelin treatment or a placebo injection of saline. Data analyzers were blinded when analyzing food journals. Intervention (if applicable): Daily injection of 12 micrograms per kilogram of Ghrelin/Saline solution administered one hour before meal and avoiding periods right before hemodialysis. Intervention groups were switched after a wash-out week. Statistical Analysis: Paired t-tests were used for comparing energy intakes at study meals against average daily intake. Multiple blood pressure readings taken within first hour of on study days were analyzed by analysis of variance. Daily home blood pressure readings were averaged within patients. Baseline and 1 hour time points compared by paired sample t-test.

Data Collection Summary	Timing of Measurements: Energy intake was measured at study meal day one after ghrelin/placebo injections and study meal day 8 before ghrelin/placebo injections. Ghrelin and acyl ghrelin levels in plasma were measured at time of injection, 30 minutes later subjects began to eat their meal and the levels were checked a second time, and levels were re-checked 30 minutes after meal began. Participants recorded daily intake in food diaries. Cytokines and routine lab work was done twice a week. Activity thermogenesis was measured to determine activity-related energy expenditure. Free-living heart and motion monitors were attached to each participant's chest wall and activity was measured througout each study week. Blood pressure was recorded during days 1 and 8 study meals during the first hour. Patients also monitored their own blood pressure throughout the week. Glucose and insulin were also measured 30 minutes before mealtime, at mealtime, and 30 minutes from start of meal. Dependent Variables: Energy intake, Ghrelin/acyl ghrelin plasma levels, blood pressure, glucose and insulin, Cytokines, Hemoglobin, Albumin, Cholesterol, C-reactive protein, Calcium, Phosphorus, interleukin 6, tumor necrosis factor alpha, lymphocyte count, neutrophil count, and alkaline phosphatase. Independent Variables: Daily injections of 12 micrograms per kilogram Ghrelin/Saline solution. Control Variables: Meal at study meal was selected so that each participant gave their meal a medium palatbility score. Same meal was used throughout study. Meals were nutritionally similar and served well within excess of expected intake. Food diaries used by participants to record intake at home were analyzed using Dietplan 5 before unmasking the randomization. Energy expenditure was measured using Actiheart pulse and motion monitors.The relationship between heart rate and workload was individually established using a short exercise test and correlation was used to assess the monitor. Activity-related energy expenditure was calculated using branched-modelled equations that assess pulse rate and movement acording to heart rate. Radioimmune assay was used to measure ghrelin and leptin. An ELISA kit was used to measure levels of acyl ghrelin, cytokines, and tumor necrosis factor alpha.

	After one week of treatment, participants were given a wash-out week and then started on the other treatment.
Description of Actual Data Sample	Initial: 12 (9 Males 3 Females) Attrition (final N): 11 Age: 22-71 Ethnicity: Not described Other relevant demographics: 9 participants were hemodialysis, 3 were peritoneal dialysis. Months on dialysis: Range from 1-14 months Anthropometrics: Mean BMI was 24.3kg/m2 Location: Dialysis center in UK
Summary of Results	Key Findings: Energy intake increased in participants taking ghrelin for both study meals (P<0.001) as well as increased daily intake during the week (P=0.04). There was no significant difference in activity thermogenesis between the two treatments (P=0.37). On average blood pressure taken at study meals reduced 10.4 mm Hg systolic and 4.7 mm Hg diastolic (P=0.032 and 0.018 respectively). For at home readings, systolic reduced to 134.7+/-4.4 from 140.2+/-4.8 mm Hg and diastolic reduced to 78.2+/-2.4 from 83.2+/-3.2 mm Hg (P=0.049 and 0.032 for systolic and diastolic). Cytokines and other nutrition labs that were measured did not change significantly. Other Findings: Not described
Author Conclusion	Sustained improvement in energy balance in malnourished dialysis was obtained using ghrelin supplementation.
Reviewer Comments	*It's important to note that ghrelin injections remained impactful as evidenced by effect produced by daily injections of ghrelin. Participants did not build up a tolerance to ghrelin. Some limitations of this study are small sample size, and the study did not last long enough to evaluate effects on weight gain.Weight was not measured in this study as it would reflect fluid status more than nutrition status.*
Funding Source	Funded by programme grants from the MRC and Wellcome Trust and by an EUFP6 Integrated Project Grant

Quality Criteria Checklist: Primary Research

Symbols Used	*Explanation*
+	***Positive** – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	***Negative** – Indicates that these issues have not been adequately addressed.*
⊘	***Neutral** – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
17. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
18. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
19. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
20. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
41. Was the <u>research question</u> clearly stated?	1	Yes
41.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
41.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
41.3. Were the target population and setting specified?	1.3	Yes
42. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
42.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
42.2. Were criteria applied equally to all study groups?	2.2	Yes
42.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
42.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
43. Were <u>study groups comparable</u>?	3	Yes
43.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	Yes
43.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	N/A
43.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	Yes
43.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	Yes
43.5. If case control study, were potential confounding factors comparable for cases		

and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	3.5	N/A
43.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.6	N/A

44. Was method of handling <u>withdrawals</u> described?	4	Yes
44.1. Were follow up methods described and the same for all groups?	4.1	Yes
44.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
44.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
44.4. Were reasons for withdrawals similar across groups	4.4	Yes
44.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
45. Was <u>blinding</u> used to prevent introduction of bias?	5	Yes
45.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	Yes
45.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
45.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	Yes
45.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
45.5. In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
46. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
46.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
46.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	N/A
46.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
46.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
46.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	Yes
46.6. Were extra or unplanned treatments described?	6.6	Yes
46.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Yes
46.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	Yes
47. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
47.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
47.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
47.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Unclear
47.4. Were the observations and measurements based on standard, valid, and	7.4	Yes

reliable data collection instruments/tests/procedures?	7.5	Yes
47.5. Was the measurement of effect at an appropriate level of precision?	7.6	Yes
47.6. Were other factors accounted for (measured) that could affect outcomes?	7.7	Yes
47.7. Were the measurements conducted consistently across groups?		

48. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
48.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
48.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
48.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
48.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	No
48.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
48.6. Was clinical significance as well as statistical significance reported?	8.6	No
48.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
49. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
49.1. Is there a discussion of findings?	9.1	Yes
49.2. Are biases and study limitations identified and discussed?	9.2	Yes
50. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Yes
50.1. Were sources of funding and investigators' affiliations described?	10.1	Yes
50.2. Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (∅)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Academy of Nutrition and Dietetics
Evidence Analysis Library® Worksheet Template and
Quality Criteria Checklist: Primary Research

Citation	Costero O, Bajo MA, Peso GD, Gil F, Aguilera A, Ros S, Hevia C, Selgas R. Treatment of Anorexia and Malnutrition in Peritoneal Dialysis Patients with Megestrol Acetate. Advances in Peritioneal Dialysis. 2004; 20:209-212.
Study Design	Before-After Study
Class	D
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	Determine effects of Megestrol Acetate on appetite and parameters of nutrition while assessing effective dosage and side effects in patients on peritoneal dialysis (PD) for end stage renal disease (ESRD).
Inclusion Criteria	Patients over age 18 on PD.
Exclusion Criteria	No exclusions other than age and PD.
Description of Study Protocol	Recruitment: Retrospectively recruited patients from 1995-2001 from PD clinic at University Hospital La Paz and La Princesa, Madrid, Spain. Design: Before-After Study Blinding used (if applicable): N/A Intervention (if applicable): PD patients with anorexia and malnutrition (n=32) received 160 mg of Megestrol Acetate per day for a time period ranging from 1-23 months (5.93±5.12 months on average). Statistical Analysis: Paired Student T-test to evaluate continuous variables, Wilcoxon T-test was used as appropriate; $p<.05$ was considered statistically significant.
Data Collection Summary	Timing of Measurements: Weight, serum albumin, protein catabolic rate, cholesterol, triglycerides, lymphocyte count, and transferrin were measured before treatment initation, after one month of treatment, and there again after three months of treatment. Dependent Variables: Appetite, weight, nutrition parameters (serum albumin, cholesterol, triglycerides, lymphocyte count, transferrin, and protein catabolic rate), and occurrence of side effects. Independent Variables: Megestrol Acetate prescription of 160 mg per day Control Variables: Intervention group serves as their own control.

Description of Actual Data Sample	Initial: 32 (19 Males 13 Females) Attrition (final N): 32 (using intention to treat) Age: 64.1 ± 13.8 (years) Ethnicity: Not described Other relevant demographics: Mean dialysis duration: 3.93+/-3.25 years Mean Weekly Kt/V: 2.14+/-0.56 Causes of ESRD: Diabetes (n=9), Glomerulonephritis (n=5), Nephrosclerosis (n=5), Unknown (n=5), Interstitial Nephritis (n=3), Systemic Lupus Erythematosus (n=2), Polycystic Kidney Disease (n=2), Vasculitis (n=1) Anthropometrics: Initial weight of participants: 66.5+/-6.4 kg Location: University Hospitals La Paz and La Princesa, Madrid, Spain
Summary of Results	Key Findings: Megestrol acetate treatment was stopped in 27 patients for the following reasons: appetite increased (n=10), patients died from unrelated causes (n=7), appetite failed to increase (n=8), patients underwent renal transplant (n=2). Appetite increased in 68.8% of patients. Weight gain became statistically significant after three months of treatment (weight at third month: 68+/-10.4 kg; p<.05). Increase in serum albumin was not statistically significant. Protein Catabolic Rate significantly increased after three months of treatment (initial: 0.95+/-0.32 g/kg/day; third month: 1.13+/-0.45 g/kg/day; p=0.032). Cholesterol did not increase. Triglycerides, lymphocyte count, and transferrin increased in the first month of treatment , but the increase never became statistically significant. Other Findings: No patients experienced side effects of megestrol acetate dosed at 160mg per day during this study.
Author Conclusion	Megestrol Acetate dosed at 160 mg per day significantly increases appetite and weight gain, increases serum albumin non-significantly, and produces no side effects.
Reviewer Comments	*Study did not address method for assessing change in appetite, or record compliance when taking Megestrol Acetate. Discussion did not review possibility for confounding variables.*
Funding Source	Not described.

Quality Criteria Checklist: Primary Research

Symbols Used	*Explanation*
+	***Positive** – Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	***Negative** – Indicates that these issues have not been adequately addressed.*
⊘	***Neutral** – indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
21. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
22. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
23. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
24. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
51. Was the <u>research question</u> clearly stated?	1	Yes
51.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
51.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
51.3. Were the target population and setting specified?	1.3	Yes
52. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
52.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
52.2. Were criteria applied equally to all study groups?	2.2	Yes
52.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
52.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
53. Were <u>study groups comparable</u>?	3	N/A
53.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	N/A
53.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	N/A
53.3. Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	N/A
53.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using		

appropriate adjustments in statistical analysis? 53.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) 53.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.4 3.5 3.6	N/A N/A N/A

54. Was method of handling <u>withdrawals</u> described?	4	Yes
54.1. Were follow up methods described and the same for all groups?	4.1	Yes
54.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
54.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
54.4. Were reasons for withdrawals similar across groups	4.4	No
54.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
55. Was <u>blinding</u> used to prevent introduction of bias?	5	N/A
55.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	N/A
55.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
55.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	N/A
55.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
55.5. In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
56. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Select a Rating
56.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	Yes
56.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	Yes
56.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
56.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
56.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	Yes
56.6. Were extra or unplanned treatments described?	6.6	N/A
56.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Yes
56.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
57. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes
57.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
57.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
57.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes

57.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
57.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
57.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
57.7. Were the measurements conducted consistently across groups?	7.7	Yes

58. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
58.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
58.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
58.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
58.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Yes
58.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	No
58.6. Was clinical significance as well as statistical significance reported?	8.6	Yes
58.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
59. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Unclear
59.1. Is there a discussion of findings?	9.1	Yes
59.2. Are biases and study limitations identified and discussed?	9.2	No
60. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Unclear
60.1. Were sources of funding and investigators' affiliations described?	10.1	No
60.2. Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (∅)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.

Academy of Nutrition and Dietetics
Evidence Analysis Library® Worksheet Template and
Quality Criteria Checklist: Primary Research

Citation	Lucas MF, Teruel JL, Burguera B, Sosa H, Rivera M, Palomares JRR, Marcen R, Quereda C. Treatment of Uraemic Anorexia with Megestrol Acetate. Spanish Nephrology Society. 2010; 30 (6): 646-652.
Study Design	Before-After Study
Class	D
Quality Rating	☐ + (Positive) ☐ - (Negative) ☒ ⊘ (Neutral)
Research Purpose	Determine effectiveness of megestrol acetate as a treatment for anorexia in dialysis patients.
Inclusion Criteria	Patients on hemodialysis who gave concent to receive megestrol acetate treatment .
Exclusion Criteria	No exclusions.
Description of Study Protocol	Recruitment: Eighteen patients with anorexia were recruited from 99 patients being dialyazed at hemodialysis clinic at Ramon y Cajal Hospital. Design: Observational, Before-After Study Blinding used (if applicable): N/A Intervention (if applicable): 160 mg megestrol acetate daily, single dose Statistical Analysis: Student's t test, $p<0.05$ was considered significant
Data Collection Summary	Timing of Measurements: Baseline and monthly Dependent Variables: Appetite, weight gain, nutrition lab parameters (albumin, lymphocytes, creatinine, and cholesterol) Independent Variables: 160 mg megestrol acetate daily, single dose Control Variables: To diagnose anorexia, researchers used the appetite questionnaire from the HEMO and DOPPS studies. Current appetite was determined from a Likert scale with the following descriptors: very good, good, fair, poor, or very poor. Next the patients were asked if their appetite had inproved, stayed the same, or worsened in the past four weeks. Anorexia was diagnosed when a patient reported their current appetite to be fair, poor, or very poor and it had not improved or worsened in the past four weeks. Patients had dialysis three times per week, consisting of 3.5-4 hour sessions with high-flux dialysis and ultra-pure dialysis liquid. Dialysis dose was determined using

	Kt/V. Protein catabolic rate determined by Borah formula modified by Sargnet. Dry weight determined using clinical criteria. Blood samples for laboratory analysis were obtained right before first dialysis session of the week.
Description of Actual Data Sample	Initial: 18 (8 Males 10 Females) Attrition (final N): 16 Age: 40-82 Ethnicity: Not described Other relevant demographics: Months on HD: 1-163 Cause of anorexia: None (n=9), gastric ulcer with edema (n=1), heminephrectomy and sepsis (n=1), treatment with interferon (n=1), graft intolerance transplantectomy (n=1), HIV (n=1), surgery for cerebral haematoma (n=1), infection of fistula (n=1). Weight loss in two month period before treatment: 0-9 kg Three patients were noted to have diabetes and eight were noted to have a failed kidney transplant. Anthropometrics: Weight: 58.9+/-10.8 kg Location: Ramon y Cajal Hospital, Madrid, Spain; patients were outpatient status.
Summary of Results	Key Findings: Appetite reportedly increased in 81% of participants. Increases in weight, serum albumin, creatinine, and protein catabolic rate were considered to be statistically significant (P-values: <.01, <.05, <.01, <.001 respectively). Changes in lymphocytes and cholesterol were not considered to be significant. Other Findings: Possible side effects of megestrol acetate may include hyperglycemia, and inhibited secretion of adrenocorticotropic hormone.
Author Conclusion	Megestrol acetate stimulates appetite in patients on hemodialysis, this stimulation has a positive effect on weight gain and nutrition related labs. Side effects such as hyperglycemia and inhibition of ACTH should be monitored.
Reviewer Comments	*After initial dosage of 160 mg, dosage changed according to patient needs. Three patients did not experience improvement in appetite, so they received 320 mg per day. Three subjects died during the study, ten subjects stopped treatment with megestrol acetate because of appetite improvement, and three subjects*

	continued to use megestrol acetate throughout entire study.
Funding Source	Not described.

Quality Criteria Checklist: Primary Research

Symbols Used	*Explanation*
+	***Positive –*** *Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis*
--	***Negative –*** *Indicates that these issues have not been adequately addressed.*
⊘	***Neutral*** *– indicates that the report is neither exceptionally strong nor exceptionally week*

Select a rating from the drop-down menu ↓

Relevance Questions		
25. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	1	Yes
26. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	2	Yes
27. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	Yes
28. Is the intervention or procedure feasible? (NA for some epidemiological studies)	4	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
Validity Questions		
61. Was the <u>research question</u> clearly stated?	1	Yes
61.1. Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	Yes
61.2. Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	Yes
61.3. Were the target population and setting specified?	1.3	Yes
62. Was the <u>selection</u> of study subjects/patients free from bias?	2	Yes
62.1. Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	Yes
62.2. Were criteria applied equally to all study groups?	2.2	Yes
62.3. Were health, demographics, and other characteristics of subjects described?	2.3	Yes
62.4. Were the subjects/patients a representative sample of the relevant population?	2.4	Yes
63. Were <u>study groups comparable</u>?	3	N/A
63.1. Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	N/A
63.2. Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	N/A
63.3. Were concurrent controls used? (Concurrent preferred over historical		

controls.) 63.4. If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? 63.5. If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) 63.6. If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	3.3 3.4 3.5 3.6	N/A N/A N/A N/A

64. Was method of handling <u>withdrawals</u> described?	4	Yes
64.1. Were follow up methods described and the same for all groups?	4.1	Yes
64.2. Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	4.2	Yes
64.3. Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	Yes
64.4. Were reasons for withdrawals similar across groups	4.4	Yes
64.5. If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5	N/A
65. Was <u>blinding</u> used to prevent introduction of bias?	5	N/A
65.1. In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	5.1	N/A
65.2. Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2	Yes
65.3. In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	N/A
65.4. In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4	N/A
65.5. In diagnostic study, were test results blinded to patient history and other test results?	5.5	N/A
66. Were <u>intervention</u>/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were <u>intervening factors</u> described?	6	Yes
66.1. In RCT or other intervention trial, were protocols described for all regimens studied?	6.1	N/A
66.2. In observational study, were interventions, study settings, and clinicians/provider described?	6.2	Yes
66.3. Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	Yes
66.4. Was the amount of exposure and, if relevant, subject/patient compliance measured?	6.4	Yes
66.5. Were co-interventions (e.g., ancillary treatments, other therapies) described?	6.5	Yes
66.6. Were extra or unplanned treatments described?	6.6	Yes
66.7. Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	6.7	Yes
66.8. In diagnostic study, were details of test administration and replication sufficient?	6.8	N/A
67. Were <u>outcomes</u> clearly defined and the <u>measurements valid and reliable</u>?	7	Yes

67.1. Were primary and secondary endpoints described and relevant to the question?	7.1	Yes
67.2. Were nutrition measures appropriate to question and outcomes of concern?	7.2	Yes
67.3. Was the period of follow-up long enough for important outcome(s) to occur?	7.3	Yes
67.4. Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	7.4	Yes
67.5. Was the measurement of effect at an appropriate level of precision?	7.5	Yes
67.6. Were other factors accounted for (measured) that could affect outcomes?	7.6	Yes
67.7. Were the measurements conducted consistently across groups?	7.7	Yes

68. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?	8	Yes
68.1. Were statistical analyses adequately described the results reported appropriately?	8.1	Yes
68.2. Were correct statistical tests used and assumptions of test not violated?	8.2	Yes
68.3. Were statistics reported with levels of significance and/or confidence intervals?	8.3	Yes
68.4. Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4	Yes
68.5. Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	8.5	Yes
68.6. Was clinical significance as well as statistical significance reported?	8.6	Yes
68.7. If negative findings, was a power calculation reported to address type 2 error?	8.7	N/A
69. **Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?**	9	Yes
69.1. Is there a discussion of findings?	9.1	Yes
69.2. Are biases and study limitations identified and discussed?	9.2	Yes
70. Is bias due to study's <u>funding or sponsorship</u> unlikely?	10	Unclear
70.1. Were sources of funding and investigators' affiliations described?	10.1	No
70.2. Was there no apparent conflict of interest?	10.2	Yes

MINUS/NEGATIVE (-)
If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.

NEUTRAL (∅)
If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Evidence Worksheet.

PLUS/POSITIVE (+)
If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.