# Anorexia in hemodialysis patients: An update

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**Anorexia, defined as the loss of the desire to eat, is relatively common in hemodialysis (HD) patients, occurring in one-third of cases. The pathogenesis is essentially unknown. It has been proposed that uremic toxins as middle molecules, inflammation, altered amino-acid pattern, leptin, ghrelin, and neuropeptide Y are involved. Anorexia reduces oral energy and protein intakes, thus contributing to the development of malnutrition and cachexia. Unquestionably, it contributes to poor quality of life. The clinical relevance of anorexia as an independent prognostic factor in HD patients is a matter of debated issue. The treatment of this debilitating condition is based on a therapeutic strategy which may include daily dialysis sessions and nutritional counseling. Normalization of plasma branched-chain amino acids through branched-chain amino acids supplementation may decrease anorexia and improve energy and protein intake. The role of megestrol acetate as appetite stimulant needs to be validated through adequate randomized trials. Subcutaneous ghrelin administration and melanocortin-receptor antagonists appear promising therapeutic interventions.**

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Malnutrition is highly prevalent in hemodialysis (HD) patients and significantly affects morbidity and mortality.[1] Inadequate dietary intake, secondary to anorexia, underlying illness, taste abnormalities, loss of dentures, gastropathy, enteropathy, medications, psychosocial conditions, aging and HD-related factors, are some of the most frequent and important causes of malnutrition in HD patients.[1–2]

Anorexia, defined as the loss of the desire to eat, is relatively common in HD patients, contributes largely to malnutrition, affects quality of life, and is associated with an increased risk of morbidity and mortality.[1–2]

The present review will discuss the clinical features, possible pathogenic mechanisms and treatment of this debilitating condition.

## PREVALENCE

Anorexia is present in about one-third of HD patients. Kalantar-Zadeh *et al.*[3] have shown that diminished appetite was reported in 124 out of 331 (38%) HD patients and that, of these, 7% had poor appetite and 31% had fair appetite, and none complaining to suffer from very poor appetite. Similarly, in the Hemodialysis (HEMO) Study, one-third of 1846 HD patients included in the trial reported a diminished appetite: fair in 23.8% and poor or very poor in 8.8%.[4] Similar to these data, Bossola *et al.*[2] have recently shown, that anorexia was present in 37.8% of cases. Interestingly, Burrowes *et al.*[5] reported that an higher percentage of patients had poor or very poor appetite on dialysis treatment days (12.7%), than on non-dialysis treatment days (5.4%). As consequence, the mean weight-adjusted dietary energy and protein intake diminished significantly from non-dialysis treatment days to dialysis treatment days from 77.5 kcal/day to 4.79 g/day. An energy deficit of 77.5 kcal per dialysis treatment days amounts to an estimated annual deficit of 12 500 kcal and this translates into significant lower dietary energy and protein intake.

## DIAGNOSTIC TOOLS

The presence of anorexia and its degree can be evaluated through the first three questions of the Appetite and Diet Assessment Tool.[3–4] The responses to the first question, *During the last week, how would you rate your appetite?*, adhered to a five-point Likert scale: (1) very good, (2) good, (3) fair, (4) poor, and (5) very poor. The second and third questions ask whether there had been a change in appetite in

the last week and, if so, whether had appetite increased, remained the same, or decreased.

Food record, diet recall or diet history are also useful tools to evaluate the presence of disturbed appetite.[1–2] The HEMO study showed that higher appetite scores were associated significantly with increasing dietary energy and protein intakes measured by 2-day diet dairy-assisted recall and dietary intakes declined steadily with poorer appetite scores.[5]

## CLINICAL EFFECTS

Anorexia reduces oral energy and protein intakes, thus contributing to the development of malnutrition and cachexia. [1–3] Anorexic patients, when compared with non-anorexic ones, had lower dietary energy, and protein intakes, lower levels of serum albumin and total lymphocytes, and a higher weight loss during the last 6 months.[2] In the study of Kalanthar–Zadeh *et al.*[3] the protein intake was progressively and significantly lower as appetite categories (poor, fair, good, very good) worsened; a similar trend was also found for blood haemoglobin, serum albumin, and prealbumin. In the HEMO Study, lower values for energy and protein intakes, serum albumin, creatinine, post-dialysis weight, and upper arm and calf circumference were observed with poorer appetite ratings.[4] Interestingly, some authors have observed a greater reduction of daily energy intake than daily protein intake in stable chronic HD patients.[6]

The clinical relevance of anorexia as an independent prognostic factor in HD is an argument of debate. Some authors have demonstrated that the mortality hazard ratio nearly doubled across each of the four worsening appetite categories (very good, good, fair, poor) and that, after the appetite categories were dichotomized, anorexia was associated with an increase ($\sim$4.5–5 times) in mortality risk.[3] On the other hand, the HEMO study reported that, after adjustment for demographic factors and randomized treatment assignments, there was a significant association between poorer self-reported appetite and death but the association became non-significant with further adjustment for comorbidity.[4] However, poorer appetite was unequivocally associated with increased hospitalization rates.[6] Unquestionably, anorexia contributes to poor quality of life. In the HEMO Study, the health-related quality of life measured by the Medical Outcomes Study Short Form-36 (MOS-SF-36) was lower among patients with poor appetite even after controlling for comorbidities and dose of HD.[7] Poor appetite was also associated with both lower Physical Component Scale and Mental Component Scale of the MOS-SF-36.

## PATHOGENESIS

The pathogenesis of anorexia in HD patients is essentially unknown. It has been proposed that uremic toxins as middle molecules, inflammation, altered amino-acid pattern, hormones (e.g. leptin and ghrelin), and neuropeptides (e.g. neuropeptide Y (NPY)) are involved.[1,8] A perturbed taste sensitivity may also have a role in reducing appetite and dietary intake in HD patients. However, the link between taste sensitivity and food consumption is largely unstudied in such patients. However, many are the mediators that might be implicated in uremic anorexia and they need to be evaluated in further adequate studies (Table 1).

**Table 1 | Mediators possibly implicated in HD-related anorexia**

| |
|---|
| *Orexigenic* |
| Ghrelin |
| Neuropeptide Y |
| Agouti-related peptide |
| *Anorexigenic* |
| Leptin |
| Cholecystokinin |
| Insulin |
| Melanocortin |
| $\alpha$-melanocyte-stimulating hormone |
| Serotonin |
| Tryptophan |
| Polypeptide YY |
| Corticotropin-releasing hormone |
| TNF-$\alpha$ |
| Interleukin-1$\beta$ |

HD, hemodialysis; TNF-$\alpha$, tumor necrosis factor-alpha.

### Middle size molecules

In 1996, Anderstam *et al.*[9] demonstrated that intraperitoneal injection of uremic plasma ultrafiltrate into normal rats inhibits ingestive behavior. The effect was not specific for one type of nutrient, but was seen to affect the intakes of carbohydrate, protein, and a mixed nutritional solution to about the same extent. The absence of an effect on ingestive behavior of the non-uremic plasma ultrafiltrate supported the conclusion that the inhibition of the uremic ultrafiltrate is a feature of uremic intoxication. The observation that the ingestion of sucrose and the mixed nutritional solution were reduced after the injection of ultrafiltrate of normal urine suggests that one or more toxic factors that are normally eliminated from the body by urinary excretion accumulate in the body fluids of patients. Uremic plasma and urine fractions with the strongest dose-dependent anorexic activity had a molecular weight of 1–5 kd. In a subsequent study, Mamoun *et al.*[10] demonstrated that a intracerebroventricular injection of 5 or 10 $\mu$l of urine middle molecule fraction inhibited carbohydrate intake by 13.4 and 41.6%, respectively and that an injection of 5 or 10 $\mu$l of uremic plasma ultrafiltrate middle molecule fraction inhibited carbohydrate intake by 22.6% and 49.5%, respectively. However, the physiological effect of middle molecules on the brain is unknown, as yet little is known about their exact molecular weight and availability to the brain. Interestingly, taking into account that doses of middle molecules fractions that effectively inhibited ingestive behavior had no effect on sexual behavior, the inhibitory effects of middle molecules seems to be specific for ingestive behavior.

### Inflammation

A strong and consistent association between anorexia and high levels of inflammatory markers has been shown by Kalantar-Zadeh *et al.*[3] in a cohort of 331 HD patients. Serum concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor-α (TNF-α) increased significantly with diminishing appetite. The values for all three inflammatory markers in patients with poor, fair, good, or very good appetite were approximately twice the upper limit for the general population. Aguilera *et al.*[11] found high TNF-α plasma levels in 97.6% of 42 peritoneal dialysis patients and showed that anorectic patients had higher TNF-α levels than non-anorectic patients. Non-anorectic patients suffering other gastrointestinal symptoms also had higher levels of TNF-α than asymptomatic patients. Indeed, it is well known that cytokines are able to inhibit appetite both in healthy conditions and in various diseases (cancer, sepsis, cardiac cachexia, chronic obstructive pulmonary disease).[12] It has been extensively demonstrated that cytokines induce anorexia by acting on meal size, meal duration, and meal frequency differentially; that specific cytokines may be transported from the periphery to the brain and cytokines generate mediators that can act on peripheral and/or brain target sites; that cytokines act directly on hypothalamic neurons proposed to participate in feeding.[12]

### Altered amino-acid pattern

The amino-acid profile in end-stage renal disease (ESRD) with or without dialysis exhibits abnormal patterns, such as reduced essential/non-essential amino-acids ratio and lower branched amino acids (BCAA) levels.[13] It is well known that the behavioral outcome of deficiencies of essential amino acids and BCAA is an anorectic response.[14] Reports of anorexia with essential and branched chain aminoacids deficiency in animal models date from the early 1900 s.[14] Indeed, anorectic HD patients have significantly lower BCAA levels than non-anorectic patients.[15] Recently, it has been proposed that the low essential and branched chain amino-acids plasma and cerebrospinal fluid concentrations permits a high level of tryptophan transport across the blood–brain barrier, causing an increase in the synthesis of serotonin responsible for appetite inhibition.[16] This hypotheses, named 'peak-concentration', is still unproved in HD patients. Indeed, plasma tryptophan levels in hemodialysed patients have been shown to be lower than healthy individuals.[17] However, it is well known that hyperammonemia increases the uptake of tryptophan into the brain by activation of the L-system carrier.[18]

### Leptin, ghrelin, and NPY

Under normal conditions, energy intake is controlled by the hypothalamus where peripheral signals convey information on energy and adiposity status.[19] In the hypothalamus, the arcuate nucleus contains specific neuronal populations that transduces these inputs into neuronal responses and, via second-order neuronal signaling pathways, into behavioral responses.[19] Some signals coming from the periphery (adipose tissue and gastrointestinal tract), such as leptin and ghrelin, are perturbed in HD patients.[1,20] In fact, both plasma levels of leptin and ghrelin are significantly higher in HD patients than in controls.[1,20] Leptin, a hormone secreted from adipose tissue as a product of the *ob* gene expressed predominantly by adipocytes, influences energy homeostasis, immune, and neuroendocrine function. Leptin decreases appetite, in part, by inhibiting neurons that produce the NPY and the agouti-related peptide, that are orexigenic peptides, whereas it stimulates neurons in the arcuate-nucleus region of the hypothalamus to produce melanocortins, that are anorexigenic.[19] On the basis of the observation that ESRD patients with or without dialysis have inappropriately high serum leptin levels, it has been speculated that hyperleptinemia in ESRD patients may be one of the factors mediating anorexia and wasting.[19] Moreover, through an elegant experimental study, Cheung *et al.*[21] have shown that leptin receptor-deficient (db/db) mice, undergoing subtotal nephrectomy and consequently showing elevated circulating leptin levels, resisted the cachexic effects of uremia on weight gain, body composition, and metabolic rate. According to the authors, these results further argue towards the hypotheses that elevated circulating levels of cytokines such as leptin may be an important cause of uremia-associated cachexia via signaling through the central melanocortin system. However, although some clinical studies have demonstrated that leptin contributes to malnutrition, others have failed to demonstrate any relationships between serum leptin and different nutritional markers and intakes.[20] Moreover, Bossola *et al.*[22] confirmed that HD patients have higher levels of serum leptin than healthy subjects and demonstrated that serum leptin levels and the serum leptin/body mass index ratio were not different in anorexic and in non-anorexic HD patients. No statistically significant differences in serum leptin levels and leptin/body mass index ratio were observed between patients with dietary energy intakes of $<30$ or $\geqslant 30$ kcal/kg/day and between those with a protein intake of $<1.2$ or $\geqslant 1.2$ g/kg/day. It is possible that a state of relative leptin resistance may occur in ESRD patients receiving HD like in obese patients who do not respond to these increased leptin levels with reduced food intake. This issue has been recently reviewed by Munzberg and Myers.[23]

Ghrelin, an orexigenic peptide released primarily from the oxyntic cells of the stomach, regulates feeding, and body weight regulation through stimulation of hypothalamic appetite centers and coordination of energy balance.[19] A common observation is that plasma ghrelin levels are markedly increased in HD patients with respect to controls.[24] Chang *et al.* have determined the profile of plasma ghrelin levels over 24 h in non-diabetic HD patients showing a unique diurnal change without an obvious plasma ghrelin rise before each meal time and not a rapid fall after eating.[25] They also found that the average level of plasma ghrelin in HD patients was one-fifth higher than in the healthy control group at most sampling times during the day, except between

1000 and 1400 According to the authors of the study, these observations suggest that there is a resistance to ghrelin action in ESRD patients, either peripheral or central, or both. The detection of high plasma ghrelin levels in HD patients is in contrast with the strong tendency of HD patients to be anorexic. Interestingly, no association was found between plasma ghrelin levels and estimated protein intake in HD patients[24] whereas Aguilera *et al.*[26] have recently demonstrated that plasma ghrelin levels are elevated in peritoneal dialysis patients and that the anorexic ones showed relatively lower values of ghrelin than did obese patients or patients with normal appetite. Overall, it seems that the available data do not allow definitive and clear considerations on the significance of high plasma ghrelin level as well as on its role in the perturbation of feeding behavior that occurs in many HD patients.

NPY is the most potent orexigen factor known.[19] Unfortunately, there are no studies in HD patients who have evaluated the plasma NPY levels and none have correlated them with the presence of anorexia and with nutritional parameters. Lower than normal NPY plasma values have been shown in 22% of peritoneal dialysis patients, normal values in 66%, and high values in 12%.[11] NPY values were lower in anorexic ($43.2 \pm 27.5$ pg/ml) than in non-anorexic patients ($64.9 \pm 25.5$; $P < 0.05$). Patients with gastrointestinal symptoms also showed lower values than those without. Interestingly, the NPY plasma levels had a significant inverse correlation with plasma TNF-$\alpha$ levels.

## TREATMENT

The treatment of anorexia in HD patients is based on a therapeutic strategy which may include frequent dialysis sessions, nutritional counseling, and nutritional and pharmacological approaches (Table 2).

### Increase in number of dialysis sessions

The increase in the number of dialysis sessions through daily HD has been shown to improve appetite and food intake.[27] This is probably owing to a general feeling of well-being, increased physical activity, fewer dietetic restrictions, decreased dose of medications such as phosphate binders and antihypertensive drugs. It has also been suggested that daily HD increases the clearance of potential anorexic factors.[27] Moreover, it seems that daily HD significantly increases serum albumin and cholesterol levels, and dry body weight.[27]

With conventional thrice weekly regimens, the dialysis dose increase or the use of high dialysis flux does not seem to improve appetite and dietary intake. In the HEMO study, self-reported appetite rating did not differ significantly in either the dialysis dose or membrane flux treatment groups. This translated in similar dietary energy and protein intakes.[4–5]

Although no specific data exist about the effect of hemodiafiltration, acetate-free biofiltration, and biofeedback technique on appetite and dietary intake, it is possible that, based on their better depuration and control of intradialytic symptoms, they could influence HD-related anorexia. However, it remains to be defined through adequate studies if these techniques might have a significant role in improving appetite, dietary intake, and ultimately nutritional status.

### Nutritional counseling

A comprehensive nutritional, diet and appetite assessment to identify if nutritional status is too low is mandatory and so is the definition of problems related to self-feeding, access to food, gastrointestinal distress, and eventually, it is necessary to identify active psychic, social, medical, dialytic, or medicinal-related issues that could affect food intake.[1–2] Dietary counseling to correct reduced or unhealthy nutrient intake, performed by a nutritionist has been shown to be useful. Akpele and Bailey[28] have recently demonstrated in stable HD patients with inadequate dietary intake that the rate of change in serum albumin level was significantly greater among patients randomized to receive intensive nutritional counseling than among those who received oral supplements. On average, the serum albumin level increased 0.06 g/dl per month for patients randomized to the dietary

**Table 2 | Actual and potential therapeutic interventions for anorexia of dialysis patients: results of clinical studies**

| Author | No. of patients | Type of intervention/ treatment | Duration | Effects |
|---|---|---|---|---|
| Akpele and Bailey[28] | 40 | Dietary counseling | 14 months | Serum albumin increase |
| Burrowes *et al.*[29] | 1 | Megestrol acetate | 320 mg/day for 24 weeks | Improvement of reported appetite, increase of energy and protein intakes, fat mass increase, decrease of fat-free mass |
| Boccanfuso *et al.*[30] | 17 | Megestrol acetate | 400 mg BID for 6 months | Improvement of appetite and increase of dry weight |
| Rammohan *et al.*[31] | 10 | Megestrol acetate | 400 mg/day for 16 weeks | Improvement of appetite, energy and protein intake, quality of life |
| Williams *et al.*[32] | 18 | Megestrol acetate | 160 mg/day for 3 months | No significant increase in serum albumin and lean body mass |
| Hiroshige *et al.*[15] | 28 | Oral supplementataion of branched chain amino acids | 12 g/day for 12 months | Anorexia and dietary intake improvement. Increase in serum albumin levels and anthropometric indices |
| Wynne *et al.*[19] | 9 (peritoneal dialysis patients) | Subcutaneous ghrelin | One single administration | Increase of energy intake over the following 24 h |

counseling and decreased 0.04 g/dl per month for those randomized to the dietary supplement group.

### Appetite stimulants

Megestrol acetate (MA) is a synthetic, orally active derivate of the naturally occurring hormone progesterone. MA may induce appetite via stimulation of NPY in the hypothalamus, modulation of calcium channels in the ventromedial hypothalamus, a well known satiety center, and inhibition of the activity of proinflammatory cytokine such as interleukin-1, interleukin-6, and TNF-$\alpha$[1] MA has been found to improve appetite, caloric intake, and nutritional status in cancer patients.[1] Few studies has been conducted in HD patients.[29–32] After administration of a moderate dose of MA ($\geqslant$320 mg/day) to a chronic HD patient, a fat mass increase (by 163%) and a fat-free mass decrease (by 10.6%) as consequence of improvement of reported appetite and increases of energy and protein intakes has been observed.[29] MA administered long term in 17 HD patients and in three of these for 5–6 months, improved appetite and an increase in dry weight was reported.[30] Rammohan *et al.*[31] demonstrated, in 10 hypoalbuminemic dialysis patients, that the daily administration of 400 mg of MA solution for 16 weeks improved appetite, protein and energy intake, and quality of life. Williams *et al.*[32] conducted a double-blind, crossover study in 24 HD patients with poor appetite and serum albumin less than 4 g/dl who received MA (160 mg/day) or placebo for 3 months and then switched to the other therapy. Four patients withdrew because of diarrhea and two died owing to comorbid conditions. In the 18 patients completing the study, no significant increase in albumin or lean body mass was observed. It is well known that MA can induce many side effects such as headaches, dizziness, confusion, diarrhea, hyperglicemia, thromboembolic phenomena, breakthrough uterine bleeding, peripheral edema, hypertension, adrenal suppression, and adrenal insufficiency.[1] On the basis of these considerations, it seems that the use of MA in the clinical practice cannot be recommended. Large, randomized, controlled trials are warranted to really define the exact role of MA in preventing and treating anorexia in HD patients.

### Oral BCAA supplementation

Hiroshige *et al.*[15] randomly assigned 28 malnourished patients with anorexia and low-plasma albumin levels to the administration of BCAA supplementation (12 g/day) or placebo. In patients receiving BCAA supplementation, anorexia, and poor oral and protein, and caloric intakes improved within a month concomitant with the improvement in plasma BCAA levels over the values in well-nourished patients. After 6 months of BCAA supplementation, anthropometric indices showed a statistically significant enhancement and serum albumin levels increased from 3.3 g/dl to 3.9 g/dl. After exchanging BCAA for placebo, spontaneous oral food intake decreased, although the favorable nutritional status persisted for the next 6 months.

These data, although preliminary, suggest that normalization of plasma BCAA levels may decrease anorexia and improve energy and protein intake in HD patients. However, they need to be validated in larger trials.

### Perspectives

Although plasma ghrelin levels are increased in dialysis patients, a single subcutaneous administration of ghrelin has been shown to determine a twofold increase in short-term energy intake for each individual in a cohort of mild-to-moderate malnourished peritoneal dialysis patients (the mean energy intake increased from $440 \pm 80$ to $690 \pm 60$ kcal), and this increase was followed by a trend toward increased energy intake over the following 24 h.[33] Interestingly, there was no subsequent compensatory reduction in energy intake over the following 72 h. Ghrelin administration resulted in a significant decrease in mean arterial blood pressure, without, however, symptomatic hypotension or reflex tachycardia. It remains to be defined if long-term ghrelin administration may have the potential to improve nutritional status and patients' outcome. Further randomized, controlled studies are warranted to define if subcutaneous ghrelin may have a role in the treatment of anorexia of HD patients. The central melanocortin system has been recognized as an important regulator of energy balance for several years.[34] Activation of hypothalamic MC4 receptor by the endogenous agonist $\alpha$-melanocyte stimulating hormone decreases food intake and leads to an increase in energy expenditure, whereas blockade of the MC4 receptor by the endogenous MC4-R inverse agonist, the agouti-related protein, increases food intake, decreases energy expenditure and leads to weight gain.[34] It has been demonstrated, in experimental studies, that MC4-R blockade through the central administration of agouti-related peptide or the MC3/4-R antagonist SHU-9119 protect animals against uremic anorexia and cachexia.[21] MC4 antagonists appear an attractive therapeutic approach for the anorexia-cachexia syndrome and may have a role also in ESRD patients receiving maintenance HD.

## CONCLUSION

Anorexia, relatively common in HD patients, has detrimental effects on the nutritional status, the quality of life and survival. The therapeutic armamentarium is relatively poor. There is an acute necessity for trials with most drugs and nutritional tools for complete validation. Promising seems the role of ghrelin and melanocortin-receptor antagonists. However, further studies are urgently needed to better understand the pathogenic mechanisms of HD-related anorexia and to see if amelioration of anorexia and improvements in energy intake would result in a long-term benefit in terms of increased quality of life and reduced morbidity and mortality.

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