Leptin and Nutritional Status in Patients with CKD

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The prevalence of protein-energy malnutrition (PEM) in patients with chronic kidney disease (CKD) is well documented and is a strong predictor of morbidity and mortality (1-3). Barriers to maintaining adequate nutritional status include decreased appetite, reduced palatability of foods, accumulation of uremic toxins, co-morbid illnesses and inflammatory conditions (1, 4-6). Rates of malnutrition remain high in this population despite interventions to increase calorie and protein intake including oral nutrition supplements, amino acid-enriched peritoneal dialysis solutions, total parenteral nutrition (TPN) and tube feedings (3).

Findings from several studies indicate that elevated serum levels of cytokines in patients with CKD may have a negative impact on appetite, food intake and nutritional status (2,7,8). Leptin, a member of the interleukin (IL)-6 family of cytokines, increases significantly in some patients with CKD and has been linked to changes in nutrition intake and body composition in this population (8,9,10).

Considerable research efforts have been made to determine the role of leptin in malnutrition associated with CKD and to develop effective interventions for improving nutritional status. This article will review recent studies on change in leptin levels in kidney disease, the relationship between serum leptin and markers of nutritional status in patients with CKD, and therapeutic strategies for improving patient outcomes.

Change in leptin levels in kidney disease

Leptin is a 16-kDa protein secreted by adipose tissue into the bloodstream and plays an important role in body weight regulation through its effects on the centers of hunger, energy expenditure and body temperature in the hypothalamus (11). Normal serum leptin levels are 1.0 - 35.3 and 3.6 - 72.4 ng/mL in males and females, respectively (12).

In a cross-sectional study of 233 men and women ages 23 to 75 years with intact renal function, subjects were divided into five categories of body mass index (BMI) from normal weight (BMI <25 kg/m^2) to severely obese (BMI ≥40 kg/m^2) (13). Serum leptin level was directly associated with BMI and waist circumference, and there was a linear increase in mean leptin level across the five categories of BMI. Serum leptin levels were significantly higher in women, regardless of BMI and waist circumference. Findings from this study suggest that in the non-renal population, serum leptin levels are correlated with body fat mass and women have higher leptin levels than men.

In patients with diabetes or excess body weight, the appearance of >30 mg albumin/day in the urine, referred to as microalbuminuria, is an early indicator of kidney disease (14,15). If microalbuminuria is untreated, macroalbuminuria (albumin excretion ≥300 mg/day) may develop, followed by a decrease in glomerular filtration rate (GFR). In a study designed to determine whether serum leptin levels were elevated in patients with type 2 diabetes and microalbuminuria or macroalbuminuria, 60 subjects were assigned to two study groups (15). One group contained 10 patients with type 2 diabetes and macroalbuminuria, 10 patients with type 2 diabetes and normoalbuminuria, and 10 healthy controls. The second group contained 10 patients with type 2 diabetes and microalbuminuria, 10 patients with type 2 diabetes and normoalbuminuria, and 10 healthy controls. Subgroups within both study groups were matched for sex and body fatness. In the first group, macroalbuminuric patients had higher leptin levels (11.90±2.98 ng/mL) than normoalbuminuric patients (4.13±0.92 ng/mL) and healthy controls (4.78±1.37 ng/mL). In the second group, microalbuminuric patients had higher leptin levels (21.16±5.80 ng/mL) than normoalbuminuric patients (8.74±1.89 ng/mL) and healthy controls (10.06±3.00 ng/

mL). After adjusting for body fatness, serum leptin levels and creatinine clearance were inversely correlated in both groups.

In a more recent study, presence of microalbuminuria and serum leptin levels were determined in 29 males (mean age 37.7±9.3 years) with abdominal obesity but without disturbances of carbohydrate metabolism or CKD (16). Microalbuminuria was detected in 62% of study participants. As rates of albumin excretion increased, serum leptin levels rose. Although serum creatinine levels were within normal limits, renal filtration function was impaired in obese patients with microalbuminuria.

The results of these studies indicate that serum leptin levels are elevated in type 2 diabetic patients with microalbuminuria and macroalbuminuria, and in obese patients with microalbuminuria. These findings suggest that leptin metabolism begins to change in the early stages of kidney disease.

Several studies have investigated leptin levels in patients with CKD. In a study of 219 patients with various degrees of renal failure, serum leptin levels were negatively correlated with GFR (17). In a small study of 36 patients with CKD Stage 5, leptin levels corrected for BMI were four times higher than in healthy controls (18). Other studies have shown significantly higher leptin levels in patients undergoing peritoneal dialysis (PD) than in patients on maintenance hemodialysis (HD) or in uremic patients on conservative management, and marked increases in serum leptin levels within three months of initiation of PD therapy (19,20). Thus, findings from these studies indicate that clearance of leptin from the blood decreases as kidney failure progresses, resulting in high serum leptin levels known as hyperleptinemia.

Leptin levels and markers of nutritional status in patients with chronic kidney disease (CKD)

Reduced renal clearance of leptin in CKD leads to elevated serum leptin, which has been identified as a potential cause of anorexia and poor nutritional status in this population (8-10). Serum leptin concentration was significantly related to BMI and skinfold thickness in an elderly polypathological population (21) and a number of studies have investigated the relationship between serum leptin levels and markers of nutritional status in patients with CKD.

In one study, serum leptin was measured by radioimmunoassay and body composition was determined by dual-energy X-ray absorptiometry (DEXA) in 23 undialyzed patients with CKD, 24 PD patients and 22 HD patients (10). Dietary intake was monitored using 3-day diet diaries. All subjects were Caucasian and free from diabetes, and 24 people with intact renal function served as controls. Leptin relative to total fat mass was significantly higher in patients than in controls, particularly in patients undergoing maintenance dialysis. One-third of the dialysis patients were consuming less than prescribed amounts of calories (30-35 kcal/ kg ideal body weight [IBW]) and protein (1.1-1.3 g/kg IBW for PD patients and 1.1-1.2 g/kg IBW for HD patients). Dialysis patients with the highest leptin to fat mass ratio had the lowest daily protein intake and significantly less lean tissue mass than other patients and controls. This data suggests an association between increased leptin levels, low protein intake and loss of lean tissue in patients undergoing maintenance dialysis therapy.

In another study of nutritional status in nondiabetic patients undergoing maintenance dialysis therapy, BMI, fat mass, lean body mass, serum albumin, leptin and total protein were determined in 32 patients undergoing continuous ambulatory peritoneal dialysis (CAPD) and 152 HD patients (22). While no significant difference was found between CAPD and HD patients with respect to serum leptin levels, female patients in both groups had significantly higher leptin levels than males. Serum leptin levels in both male and female CAPD and HD patients showed significant positive correlation with age, fat mass, BMI and triceps skinfold thickness. No correlation was found between serum leptin levels and lean body mass, serum albumin or total protein in this study.

Other studies have focused on the impact of serum leptin on body composition in HD patients. When serum leptin levels were measured in 103 HD patients and 167 age- and gender matched healthy controls, HD patients had significantly higher leptin levels and significantly lower fat mass and lean mass than controls (23). In both HD patients and controls, leptin levels were significantly higher

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in females than in males and correlated positively with percent body fat. After assigning all subjects to one of six categories based on percent body fat and comparing leptin levels in HD patients and controls in each category, leptin was significantly higher in HD patients than controls only in percent body fat categories of 30 or greater.

In an investigation of the association between weight loss and leptin levels in a population of HD patients, serum leptin, BMI and body fat mass were compared in 181 patients undergoing HD and 185 healthy controls (24). Findings from this study revealed no significant difference in leptin levels between HD patients and controls but BMI in HD patients was significantly lower than BMI in controls. In the HD patients, serum leptin to fat mass ratio showed a significant inverse correlation with duration of HD and a high ratio of leptin to fat mass was associated with weight loss during a 17-month follow-up period.

While there appears to be a close relationship between serum leptin levels and body fat mass in maintenance dialysis patients, the association between leptin levels and symptoms of anorexia in this population is less well defined. In a prospective study directed to determine whether hyperleptinemia was associated with anorexia in maintenance HD, 49 HD patients were categorized as anorexic or non-anorexic on the basis of responses to a questionnaire discriminating for the presence of anorexia-related symptoms (25). When compared with 24 healthy control subjects, HD patients had significantly higher serum leptin levels and serum leptin to BMI ratio was significantly higher in HD patients than in controls. Although calorie and protein intake, serum albumin and mid-arm muscle circumference (MAMC) were significantly lower in anorexic than in non-anorexic patients, serum leptin levels and leptin to BMI ratios were similar in both categories of HD patient.

A cross-sectional study of 49 CAPD patients and 27 healthy controls examined serum leptin levels, body composition and dietary intake (26). Again, serum leptin was significantly higher in dialysis patients than in controls, and patients exhibited a greater increase in serum leptin for any given increase in BMI. However, no significant correlation was found between serum leptin concentration and dietary intake of calories or protein, or serum levels of albumin and prealbumin.

Collectively, these studies indicate a significant relationship between serum leptin levels, BMI and fat mass in patients undergoing maintenance dialysis therapy. Nevertheless, etiology of anorexia in this population appears to be more complex and few studies suggest a causal relationship between increased serum leptin levels and development of anorexia. Uremic toxins, inflammation and changes in amino acid profile, as well as imbalances in leptin, ghrelin and neuropepetide Y levels, are all implicated in anorexia in patients with CKD (27,28).

Therapeutic strategies for modulating serum leptin levels in CKD

Leptin levels appear to be improperly regulated in patients with CKD and may impair nutritional status in this population. Administration of anabolic agents including recombinant human growth hormone (rhGH) to patients with CKD has been linked with an increase in dietary protein intake and lean body mass, and several small studies have explored the effects of these agents on leptin regulation in CKD (29,30). Insulin-like growth factor (IGF) is associated with decreased serum leptin levels in CKD patients, while a combination of rhGH and IGF increased serum leptin levels in eight well nourished maintenance HD patients (31,32). Malnourished HD patients treated with rhGH showed increased serum leptin levels only in the presence of high insulin levels accompanying the administration of intradialytic parenteral nutrition (IDPN) (33).

Use of dialysis solutions enriched with amino acids has resulted in increased IGF levels and improved serum albumin in malnourished CAPD patients (3). When the impact of an amino acid-based dialysis solution on leptin levels was evaluated in nine stable CAPD patients, hyperleptinemia was transiently lower after three months (34). Total body mass, BMI, serum albumin and total protein all increased significantly during treatment with the amino acid-based dialysis solution but incidence of anorexia and daily energy and protein intake showed no significant changes.

A recent study of 39 malnourished HD patients assessed the effect of high-calorie supplementation on serum leptin

levels (35). Twelve patients received an additional 475 kcal and 16 grams of protein daily and 27 patients received an additional 67 kcal and 16 grams of protein daily for 12 weeks. Sixteen age- and sex-matched well nourished patients not given nutritional supplementation served as controls. Patients receiving high-calorie supplementation showed significant increases in body fat mass and serum leptin levels. Findings from a study designed to evaluate response of a small group of hypoalbuminemic dialysis patients to the appetite stimulant megestrol acetate included progressive increase in serum leptin levels, improved appetite and increase in body weight, BMI, TSF and serum albumin (36).

These more recent studies indicate that increased serum leptin levels in maintenance dialysis patients may parallel an improvement in nutrition intake and markers of nutritional status, including body weight and serum albumin. However, leptin is likely only one of many factors in the development of malnutrition during CKD. Increased understanding of other mechanisms regulating appetite and food intake may lead to new therapies for improving nutritional status in patients with CKD.

References:

1. Mehrotra R, Kopple JD. Nutritional management of maintenance dialysis patients: Why aren't we doing better? *Annu Rev Nutr.* 2001;21:343-79.
2. Bergstrom J. Mechanisms of uremic suppression of appetite. *J Ren Nutr.* 1999;9:129-132.
3. Wolfson M. Effectiveness of nutrition interventions in the management of malnourished patients treated with maintenance dialysis. *J Ren Nutr.* 1999;9:126-128.
4. Kaysen GA. Biological basis of hypoalbuminemia in ESRD. *J Am Soc Nephrol.* 1998;9:2368-2376.
5. Sehgal AR, Leon J, Soinski JA. Barriers to adequate protein nutrition among hemodialysis patients. *J Ren Nutr.* 1998;8:179-187.
6. Dobell E, Chan M, Williams P, Allman M. Food preferences and food habits of patients with chronic renal failure undergoing dialysis. *J Am Diet Assoc.* 1993; 93: 1129-1135.
7. Libetta C, De Nicola L, Rampino T, De Simone W, Memoli B. Inflammatory effects of peritoneal dialysis: Evidence of systemic monocyte activity. *Kidney Int.* 1996;49: 506-511.
8. Guarnieri G, Antonione R, Biolo G. Mechanisms of malnutrition in uremia. *J Ren Nutr.* 2003;13:153-157.
9. Mak RH, Cheung W, Cone RD, Marks DL. Leptin and inflammation-associated cachexia in chronic kidney disease. *Kidney Int.* 2006;69:794-797.
10. Young GA, Woodrow G, Kendall S, Oldroyd B, Turney JH, Brownjohn AM, Smith MA. Increased plasma leptin/fat ratio in patients with chronic renal failure: A cause of malnutrition? *Nephrol Dial Transplant.* 1997;12:2318-2323.
11. Barazzoni R, Biolo G, Zanetti M, Bernardi A, Guarnieri G. Inflammation and adipose tissue in uremia. *J Ren Nutr.* 2006;16:204-207.
12. Specialty Laboratories Test Menu #4891: Leptin. Available at http://www:specialtylabs.com/tests/details.asp?id=4891. Accessed March 2007.
13. Monti V, Carlson JJ, Hunt SC, Adams TD. Relationship of ghrelin and leptin hormones with body mass index and waist circumference in a random sample of adults. *J Am Diet Assoc.* 2006;106:822-828.
14. Rutkowski P, Klassen A, Sebekova K, Bahner U, Heidland A. Renal disease in obesity: The need for greater attention. *J Ren Nutr*. 2006;16:216-223.
15. Fruehwald-Schultes B, Kern W, Beyer J, Forst T, Pfutzner A, Peters A. Elevated serum leptin concentrations in type 2 diabetic patients with microalbuminuria and macroalbuminuria. *Metabolism.* 1999;48:1290-1293.
16. Saginova EA, Fedorova EI, Fomin VV, Moiseev SV, Minakova EG, Gitel EP, Samokhodskaia LM, Kutyrina IM, Mukhin NA. Development of renal disease in obese patients. *Ter Arkh.* 2006;78:36-41.
17. Nordfors L, Lonnqvist F, Heimburger O, Danielsson A, Schalling M, Stenvinkel P. Low leptin gene expression and hyperleptinemia in chronic renal failure. *Kidney Int.* 1998;54:1267-1275.
18. Sharma K, Considine RV. The Ob protein (leptin) and the kidney. *Kidney Int.* 1998; 53:1483-1487.
19. Diez JJ, Iglesias P, Fernandez-Reyes MJ, Aguilera A, Bajo MA, Alvarez-Fidalgo P, Codoceo R, Selgas R. Serum concentrations of leptin, adinopectin and

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resistin, and their relationship with cardiovascular disease in patients with end-stage renal disease. *Clin Endocrinol (Oxf.)* 2005;62:242-249.
20. Kim DJ, Oh DJ, Kim B, Lim YH, Kang WH, Lee BH, Lee SK, Huh W, Kim SE, Lee MK, Kang SA, Oh HY. The effect of continuous ambulatory peritoneal dialysis on change in serum leptin. *Perit Dial Int.* 1999;19 (suppl 2):S172-S175.
21. Bouillanne O, Golmard JL, Coussieu C, Noel M, Durand D, Piette F, Nivet-Antoine V. Leptin a new biological marker for evaluating malnutrition in elderly patients. *Eur J Clin Nutr.* 2006; [Epub ahead of print]. Available at http://origin.www.com/ejcn/journal/vaop/ncurrent/index.html#06122006. Accessed March 2007.
22. Yilmaz A, Kayardi M, Icagasioglu S, Candan F, Nur N, Gultekin F. Relationship between serum leptin levels and body composition and markers of malnutrition in nondiabetic patients on peritoneal dialysis or hemodialysis. *J Chin Med Assoc.* 2005; 68:566-570.
23. Nishizawa Y, Shoji T, Tanaka S, Yamashita M, Morita A, Emoto M, Tabata T, Inoue T, Morii H. Plasma leptin level and its relationship with body composition in hemodialysis patients. *Am J Kidney Dis.* 1998;31:655-661.
24. Odamaki M, Furuya R, Yoneyama T, Nishikino M, Hibi I, Miyaji K, Kumagai H. Association of the serum leptin concentration with weight loss in chronic hemodialysis patients. *Am J Kidney Dis.* 1999;33:361-368.
25. Bossola M, Muscaritoli M, Valenza V, Panocchia N, Tazza L, Cascino A, Laviano A, Liberatori M, Lodovica Moussier M, Rossi Fanelli F, Luciani G. Anorexia and serum leptin levels in hemodialysis patients. *Nephron Clin Pract.* 2004;97:c76-c82.
26. Parry RG, Johnson DW, Carey DG, Hibbins M, Chang W, Purdie D, Rigby RJ. Serum leptin correlates with fat mass but not dietary energy intake in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int.* 1998;18:569-575.
27. Bossola M, Tazza L, Giungi S, Luciani G. Anorexia in hemodialysis patients: An update. *Kidney Int.* 2006;70:417-422.
28. Aguilera A, Codoceo R, Bajo MA, Iglesias P, Diez JJ, Barril G, Cigarran S, Alvarez V, Celadilla O, Fernandez-Perpen A, Montero A, Selgas R. Eating behavior disorders in uremia: A question of balance in appetite regulation. *Semin Dial.* 2004;17:44-52.
29. Ericsson F, Filho JC, Lindgren BF. Growth hormone treatment in hemodialysis patients – a randomized, double-blind, placebo-controlled study. *Scand J Urol Nephrol.* 2004;38:340-347.
30. Mehls O, Haas S. Effects of recombinant human growth hormone in catabolic adults with chronic renal failure. *Growth Horm IGF Res*. 2000;10 (suppl B):S31-S37.
31. Dagogo-Jack S, Franklin SC, Vijayan A, Liu J, Askari H, Miller SB. Recombinant human insulin-like growth factor-I (IGF-I) therapy decreases plasma leptin concentration in patients with chronic renal insufficiency. *Int J Obes Metab Disord.* 1998;22:1110-1115.
32. Fouque D, Juillard L, Lasne Y, Tabakian A, Laville M, Joly MO, Laville M. Acute leptin regulation in end-stage renal failure: The role of growth hormone and IGF-1. *Kidney Int.* 1998;54:932-937.
33. Garibotto G, Barreca A, Sofia A, Russo R, Fiorini F, Cappelli G, Cavatorta F, Cesarone A, Franceschini R, Sacco P, Minuto F, Barreca T. Effects of growth hormone on leptin metabolism and energy expenditure in hemodialysis patients with protein-calorie malnutrition. *J Am Soc Nephrol.* 2000;11:2106-2113.
34. Grzegorzewska AE, Wiecek A, Mariak I, Kokot F. Amino-acid-based dialysis solution changes leptinemia and leptin peritoneal clearance. *Adv Perit Dial.* 2000;16: 7-14.
35. Hung SC, Tung TY, Yang CS, Tarng DC. High-calorie supplementation increases serum leptin levels and improves response to rHuEPO in long-term hemodialysis patients. *Am J Kidney Dis.* 2005;45:1073-1083.
36. Rammohan M, Kalantar-Zadeh, Liang A, Ghossein C. Megestrol acetate in moderate dose for the treatment of malnutrition-inflammation complex in maintenance dialysis patients. *J Ren Nutr.* 2005;15:345-355. ◆