ADVANCES IN PRACTICE:
IMPACT OF GHRELIN ON NUTRITIONAL STATUS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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The high incidence of protein-energy malnutrition (PEM) is well documented in patients with chronic kidney disease (CKD). Its presence is a strong predictor of morbidity and mortality (1-3). Barriers to adequate nutrition intake in this population include accumulation of uremic toxins, co-morbid illnesses, inflammatory conditions, difficulty shopping for and preparing food and decreased palatability of high protein foods (1,2,4,5). In recent years attention has also focused on the roles of long and short-term regulators of appetite in the development of PEM in CKD patients (6).

Insulin and leptin are well known long-term regulators of appetite in persons with normal renal function, and both are secreted in proportion to the amount of stored body fat (7). In animal models, food intake decreases when increased insulin or leptin levels are detected in the brain. In CKD patients, elevated plasma leptin levels have been linked with decreased energy and protein intake, and loss of dry weight and lean body mass (8).

Peptides secreted by the gastrointestinal tract in response to meal size are short-term appetite regulators (7). These peptides include cholecystokinin, gastrin-releasing peptide, somatostatin and bombesin, all of which cause meal termination. Another peptide of interest is ghrelin. It was recently identified and found to promote food intake and weight gain in animals and humans (9). Adding to the interest in ghrelin is its ability to stimulate appetite and increase energy intake in cancer patients with anorexia (10).

This article will review the physiological effects of ghrelin, describe the impact of kidney disease on plasma ghrelin levels and examine the potential of ghrelin to alter nutritional status in CKD patients.

Structure and Physiological Effects

Prepro-ghrelin, the ghrelin precursor molecule, is synthesized mainly in epithelial cells lining the fundus of the stomach and consists of 117 amino acids (11,13). This precursor molecule undergoes enzymatic splitting in the cytoplasm to yield ghrelin, a 28 amino acid peptide with a molecular weight of 3315. The normal range for ghrelin levels is < 2600 g/mL. Circulating ghrelin levels are lowest shortly after eating a meal and increase prior to the next meal and during fasting (14). Ghrelin levels are decreased in obesity and elevated in cachexia (12).

Recent studies indicate that ghrelin stimulates the release of growth hormone (GH) from the anterior pituitary gland in healthy subjects and in patients with CKD (12,15). GH has previously been shown to improve serum albumin and muscle strength, promote weight gain and potentiate the effects of intradialytic parenteral nutrition (IDPN) in patients undergoing maintenance hemodialysis (16-18). Ghrelin also functions independently of GH to increase hunger through its action on the feeding center in the hypothalamus, and to suppress fat utilization in adipose tissue (12-14).

Plasma Ghrelin Levels in CKD Patients

Until recently, little was known about the metabolism and clearance of ghrelin or factors affecting circulating ghrelin levels. In a clinical study investigating the effect of kidney disease on ghrelin levels, 46 nondiabetic patients with stages 3 and 4 CKD underwent renal function measurement and radioimmunoassay of their plasma ghrelin (19). Patients with glomerular filtration rates (GFR) ≤ 30 mL/min/1.73m² had elevated ghrelin levels and there was a significant inverse relationship between plasma ghrelin level and GFR. Thus, ghrelin levels seem to increase as GFR declines.

Another study compared ghrelin levels in patients undergoing maintenance hemodialysis (HD) and healthy controls (20). Both groups were of similar age and body mass index (BMI). Ghrelin levels were significantly higher in HD patients than healthy controls (4.49±0.74 ng/mL vs. 1.79±0.15 ng/mL). In addition, HD patients had significantly higher levels of GH and leptin.

These findings were confirmed and extended by a study in which ghrelin levels in HD patients were tracked before and after meal ingestion, and before and after a dialysis treatment

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(21). Again, ghrelin levels were significantly higher in HD patients than in healthy controls. Meal ingestion induced a decrease in ghrelin levels in 5 out of 6 patients tested. HD treatment resulted in a significant decrease in circulating ghrelin, and ghrelin was in the normal range at the end of HD treatment in 4 out of 5 patients tested. Plasma ghrelin concentrations were also significantly higher in normal weight patients compared to overweight or obese patients.

Another investigation used a cross-sectional design to compare plasma ghrelin levels in 20 HD patients and 21 peritoneal dialysis (PD) patients with age-matched healthy controls (22). This study found higher plasma ghrelin levels in both HD and PD patients than in healthy controls, and a strong inverse correlation between ghrelin levels and age.

Collectively, these studies indicate that plasma ghrelin levels are elevated in patients with CKD (19-22). Higher ghrelin levels in patients with CKD compared with healthy controls might be caused by decreased excretion of ghrelin in renal failure. The fact that ghrelin circulates at higher levels in normal weight versus overweight or obese HD patients and decreases after a meal suggests that regulation of ghrelin does occur in CKD, but that secretion is shifted to a higher level.

Ghrelin and Nutritional Status in CKD Patients

Several high molecular weight compounds, including leptin and the proinflammatory cytokines, are elevated in CKD and impact nutritional status in this patient population (23). Findings from a number of studies suggest a relationship between ghrelin, appetite regulation and body composition in patients with CKD.

In an investigation of the relationship between long- and short-term regulators of appetite and food intake in PD patients, 42 patients were divided into three groups: those with anorexia, those with obesity and those with no eating behavior disorders (24). A visual analog scale was used to evaluate the motivation to eat. Thirty-six patients had mean plasma ghrelin levels above the normal range. Patients with anorexia had lower ghrelin levels and higher levels of cholecystokinin. The proinflammatory cytokines tumor necrosis factor alpha and interleukin-1 were also elevated compared to patients with normal appetite or obesity. A significant positive correlation was found between circulating plasma ghrelin levels and eating motivation.

Results from a recently completed study on energy intake in PD patients with mild to moderate malnutrition indicate that subcutaneous ghrelin administration may increase food consumption (25). Nine PD patients with a mean subjective global assessment (SGA) score of 5.7±1.7 showed significantly increased mean energy intake after receiving subcutaneous ghrelin (3.6 nmol/kg) when compared with placebo. A nonsignificant increase in energy intake over a 24-hour period following intervention was also noted.

The relationship between plasma ghrelin levels and body composition in maintenance dialysis patients has also been investigated (20,26). When HD patients were compared with healthy controls of similar age and BMI, the HD patients had significantly higher percentages of body fat, as well as higher ghrelin levels (20). In another study, a longitudinal evaluation of plasma ghrelin levels and body composition was performed in 52 patients undergoing maintenance dialysis therapy (26). This study found markedly elevated ghrelin levels in both HD and PD patients, and an inverse relationship between plasma ghrelin and circulating leptin and insulin levels. However, while fat mass increased and plasma ghrelin levels decreased after 12 months of dialysis in PD patients, there were no significant changes in either body composition or plasma ghrelin levels over the same time period in HD patients.

Summary

Plasma ghrelin concentrations increase in CKD, probably as a result of reduced renal excretion (13). This finding suggests that ghrelin may play a part in the metabolic abnormalities that develop as a result of uremia (27). A negative correlation between plasma ghrelin levels and nutritional markers suggests a causal relationship between reduced nutrition intake and increased ghrelin secretion in patients with CKD undergoing maintenance dialysis (22).

A number of studies show that malnutrition in CKD is characterized by reduced lean body mass and conservation of fat mass (28,29). The ghrelin imbalance that has been identified in patients with CKD could impact energy

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regulation and promote the changes in body composition observed in this population. Elevated ghrelin levels in CKD are associated with higher percentage of body fat and this action is the converse of the effects of leptin, which reduces lean tissue and fat mass (8,12). Thus, increasing levels of ghrelin in CKD may counteract leptin's effects (19). Subcutaneous ghrelin administration shows promise in improving short-term food intake in PD patients with mild to moderate malnutrition. Currently, measuring ghrelin levels and ghrelin administration is not routine in the CKD population. Future studies should be directed to determine the specific effects of elevated ghrelin levels on metabolism in CKD and the long-term effect on food intake of ghrelin administration.

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