control of the desire to eat and in adipogenesis via mechanisms independent of the GH pathway—mechanisms that are more likely controlled by a specific central neuronal network that is also modulated by leptin (6).

In patients with chronic renal failure, glomerular filtration rate has been shown to be inversely correlated with plasma des-acyl ghrelin concentrations, whereas no relation was found with acylated ghrelin (4). Des-acyl ghrelin does not act through the GHS-1a receptor, but it is not yet clear whether it may influence appetite in humans, because the orexigenic effect could be independent of the GH secretory pathway and could, instead, be mediated by other receptors (7). Indeed, in a recent experimental study, it was shown that des-acyl ghrelin induces a negative energy balance by decreasing food intake and delaying gastric emptying and that this effect is mediated within the hypothalamus (8). In addition, peripherally administered des-acyl ghrelin decreases food intake and disrupts the motor activity of the antrum in freely moving, conscious, fasted rats via direct activation of brain receptors after the des-acyl ghrelin crosses the blood-brain barrier, but there is no activation of vagal afferent pathways. In the brain, a selective corticotropin-releasing factor 2 receptor is involved in this action (9).

We recently conducted a study in ESRD patients to investigate whether increased des-acyl ghrelin concentrations may be implicated in the pathogenesis of hemodialysis-related anorexia (10). Our study confirmed that persons undergoing hemodialysis have significantly higher des-acyl ghrelin concentrations than do healthy subjects. Furthermore, des-acyl ghrelin concentrations are significantly higher in anorexic than in nonanorexic persons undergoing hemodialysis. Indeed, calorie intakes and fat-free mass were significantly lower in anorexic than in nonanorexic persons undergoing hemodialysis. It is interesting that the prevalence of reduced appetite was similar in the patients in our study (41%) and in those in the study of Carrero et al (44%), despite the different tools the 2 studies used to assess anorexia. These figures confirm that, in persons undergoing hemodialysis, the decrease in appetite is a clinically relevant feature that may significantly affect quality of life and outcome (2).

The hypothesis that increased des-acyl ghrelin may contribute to the development of hemodialysis-related anorexia represents another advancement in the understanding of the mechanisms underlying appetite disorders in ESRD, and it may set the stage for the development of more effective preventive and therapeutic interventions.

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Reply to A Molfino et al

Dear Sir:

We want to thank Molfino et al for their comments on our report about appetite loss in persons undergoing hemodialysis (1). We read with interest their recent publication (2) and agree on the importance of ghrelin in the regulation of appetite behavior in uremic patients. Indeed, the discovery of the different structural variants of ghrelin presents exciting new opportunities, especially after recent observations showing that des-acyl ghrelin may be more than just an innocent bystander.

To be able to better address the comments raised by Molfino et al, we measured total ghrelin concentrations in stored plasma samples (n = 223) from the same cohort of persons undergoing hemodialysis as previously studied (1). Confirming previous results (3), an inverse correlation (r = -0.25, P < 0.0001) between ghrelin and body mass index (BMI; in kg/m²) was observed. Because anorectic persons undergoing hemodialysis have low BMI, we compared the ratio of ghrelin to BMI in persons undergoing hemodialysis reporting good appetite (n = 124) or appetite loss (n = 99). In agreement with previous studies, we found that persons undergoing hemodialysis reporting loss of appetite had significantly higher ghrelin concentrations than did those reporting good appetite (437 ± 21 and 327 ± 18 pg/mL, respectively; P = 0.05). In our study, we used a radioimmunoassay method that analyzed the sum of ghrelin and des-acyl ghrelin, which presumably may account for >90% of total circulating ghrelin (4). Yoshimoto et al (4) reported that another radioimmunoassay kit that measures ghrelin alone did not find a correlation with renal function, and thus it seems conceivable that the accumulation of the structural variant of des-acyl ghrelin accounts for most of the observed increase in plasma ghrelin concentration in persons with chronic kidney disease, which confirms the findings of Molfino et al (2).

In our report, we hypothesized that sex-specific mechanisms are involved in the regulation of feeding behavior in persons undergoing hemodialysis, and we speculated that the regulation of leptin and
C-reactive protein (CRP) is a marker for inflammation. In fact, whereas a significant difference was observed in ghrelin concentrations in males and females undergoing hemodialysis who reported some degree of appetite loss (52 F, 47 M), the ratio of total ghrelin to BMI was significantly higher in the men reporting loss of appetite, but not in the women.

Ghrelin may be different in males and females. When we compared ghrelin concentrations in males and females undergoing hemodialysis who did and did not have loss of appetite, they were significantly higher in the males reporting loss of appetite, but not in the females (P = 0.01; Figure 1). It is interesting that recent data have shown that CRP may influence ghrelin concentrations (5). Thus, the higher prevalence of inflammation in anorectic males than in anorectic females in that cohort may explain at least part of the differences observed in ghrelin concentrations. In fact, whereas a significant correlation was found between ghrelin concentrations and both C-reactive protein (r = 0.16, P < 0.05) and interleukin-6 (r = 0.17, P < 0.05) in males, no such correlations were found in females, which again suggests that the associations among inflammation, appetite, and body composition should be evaluated separately in males and females. It is worth investigating whether our observations are due to the des-acyl ghrelin fraction, and that investigation may open new therapeutic perspectives in this and other populations of patients with inflammation and anorexia.

However, elevated ghrelin concentrations may represent just one of many pieces in the complicated puzzle of uremic anorexia. Clearly, this condition can arise from such diverse causes as early satiety, dysfunctional hypothalamic responses, increases in cytokine concentrations, effects of medications, and decreased taste and smell of foods. Thus, uremic anorexia represents a complex and multifactorial disorder in which many hormones and transmitters play a role, including the release of neurotransmitters (eg, serotonin) and neuropeptides (eg, neuropeptide Y and orexin) and increased production or retention of uremic toxins and gut-to-brain signaling factors (eg, cholecystokinin and ghrelin) and cytokines (eg, tumor necrosis factor-α, leptin, interleukin-6, adiponectin, and interleukin-1β) (6).

Although most uremic patients regain their appetite immediately upon the start of dialysis (which suggests the removal of ≥1 toxic factor that suppresses appetite), poor appetite is a common finding in persons undergoing dialysis. Poor appetite in persons undergoing hemodialysis is associated with higher concentrations of proinflammatory cytokines (1), which regulate the release and function of neurotransmitters affecting orexigenic and anorexigenic hypothalamic neurons. Leptin is an adipokine retained in uremia that is important in the control of metabolic rate and appetite.

Whereas some studies show that elevated circulating leptin concentrations in persons undergoing dialysis are associated with better nutritional status (perhaps reflecting leptin resistance, decreased transport of leptin across the uremic blood-brain barrier, or both), a recent study by Cheung et al (7) showed that uremic cachexia was attenuated in leptin receptor–deficient mice (db/db). This finding suggests that leptin plays a crucial role in the regulation of appetite and metabolic rate in uremia. The central effects of leptin are mediated via local activation of neurons, such as neuropeptide Y or agouti-related peptide and proopiomelanocortin, which triggers the release of α-melanocyte–stimulating hormone and melanocortin receptor-4 (MC4-R). Because this sequence of events leads to decreased food intake and increased energy expenditure, genetic or pharmacologic blockade of MC4-R may be a future treatment for uremic anorexia. Indeed, Cheung et al (7) showed that, by central blocking of MC4-R via a genetic approach, uremic anorexia was attenuated in a mice model. Adiponectin (another adipokine retained in uremic patients) has mostly been seen as a protector of vascular function; among other beneficial effects, it has been reported to inhibit the expression of adhesion molecules, stabilize plaques, suppress tumor necrosis factor-α production, and attenuate the proliferation of vascular smooth muscle. However, because elevated adiponectin concentrations were, unexpectedly, associated with greater mortality in large cohorts of patients with congestive heart failure (8) and chronic kidney disease (9), it is possible that this adipokine also has deleterious effects. Indeed, a recent study in mice showed that intracerebroventricular administration of adiponectin decreased body weight mainly by stimulating energy expenditure, and thus adiponectin may promote wasting (10). Because Agouti mice in that study did not respond to the energy-modulating effects of adiponectin, the melanocortin pathway may be the common target (10).

Anorexia is a multifactorial feature in persons undergoing dialysis that heralds poor prognosis. Many peripheral hormones retained in uremia (including ghrelin and adipocytokines) affect appetite via central signaling pathways, and thus it is not surprising that there is currently no effective treatment for this devastating condition. Indeed, the use of various nutritional strategies and appetite stimulants has so far been largely ineffective. However, recent studies suggested that hypothalamic MC4-R plays an important role in transducing cachexigenic signals in uremia, and thus oral antagonism of the central melanocortin system may represent a novel treatment approach.

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