80% (6), which is already high. Moreover, except in cases of very severe vitamin D deficiency, phosphorus absorption is scarcely influenced by vitamin D status. Second, whereas elevated serum phosphorus is indeed a risk factor for vascular calcification, there is no evidence that vitamin D doses <10 000 IU/d either elevate serum phosphorus or increase the risk of such calcification. The issue of vitamin D toxicity was exhaustively reviewed in this Journal just a few months ago (7), and Sood and Sood may find some reassurance in that report.

We draw attention further to the fact that we used native cholecalciferol (vitamin D₃), not calcitriol [1,25(OH)₂D₃], and we wish to remind Sood and Sood that cholecalciferol does not elevate serum calcitriol concentrations in anyone (8). Calcitriol concentration is a regulated quantity, under the control mainly of parathyroid hormone. Furthermore, given the 3 orders of magnitude difference in biological potency between 25(OH)D and 1,25(OH)₂D₃, even very low concentrations of 25(OH)D are able to support generous biological potency between 25(OH)D and 1,25(OH)₂D₃, even very low concentrations of 25(OH)D are able to support generous.

Over the 4-y period of our study, 5 women developed kidney stones; 1 of these women was in the vitamin D–treated group. In addition, there were 7 subjects who had myocardial infarctions, which were evenly distributed across the 3 treatment groups. Serum phosphorus was not measured, because there was no way to justify the substantial increase in cost for measurement of a variable that would not have been predicted to change.

Finally, we reject the notion that a serum 25(OH)D concentration such as the one we achieved in our study—which was well below the best estimates of primitive—ie, physiologic—concentrations. We stress that it is the serum 25(OH)D concentration that is important, not the oral dose of vitamin D₃.

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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 lower in anorexic than in nonanorexic 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