Like total ghrelin, acylated ghrelin is also lower in HD patients with cardiovascular disease

To the Editor: Recently, Carrero *et al.*[1] showed that lower total plasma ghrelin is associated with increased total and cardiovascular mortality in protein–energy wasting hemodialysis (HD) patients. However, total ghrelin includes both acylated and des-acylated forms, with different biological actions.[2]

We assessed acylated ghrelin (A-Ghr) in 20 healthy volunteers (57.00 ± 8.62 years) and 68 HD patients (61.24 ± 12.51 years, 22 diabetics). Samples were drawn before 2 years, and at the end of this period 22 HD patients suffered from coronary heart disease (CHD). Plasma A-Ghr was measured using enzyme-linked immunosorbent assay (SPI Bio, Montigny, France). White blood cell count (WBC), C-reactive protein (CRP), and albumin were also assessed.

A-Ghr did not differ between HD patients and healthy volunteers (106.40 ± 27.53 versus 120.50 ± 45.04 pg/ml, $P = 0.424$, Mann–Whitney unpaired test). A-Ghr was lower in HD patients suffering from CHD (95.00 ± 22.04 versus 111.85 ± 28.42 pg/ml, $P = 0.023$) and was positively correlated with WBC (Spearman's $\rho = 0.426$, $P < 0.001$), CRP ($\rho = 0.261$, $P = 0.023$), that is, with inflammation, and age ($\rho = 0.323$, $P = 0.007$). A-Ghr was negatively correlated with the marker of nutrition albumin ($\rho = -0.368$, $P = 0.002$).

Thus, similar to total ghrelin, A-Ghr is also lower in HD patients with cardiovascular disease. This could be simply an epiphenomenon, as in the case of cachexia that accompanies inflammation, A-Ghr increases to counteract weight-loss mechanisms, and it is well known that inflammation also induces atherosclerosis.[2,3] Alternatively, higher A-Ghr could offer protection from atherosclerosis through its direct action on the endothelium or indirectly by attenuating inflammation.[2,4] The second case, if proved true, is promising for pharmaceutical intervention in the near future.

1. Carrero JJ, Nakashima A, Qureshi AR *et al.* Protein-energy wasting modifies the association of ghrelin with inflammation, leptin, and mortality in hemodialysis patients. *Kidney Int* 2011; **79**: 749–756.
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The Authors Reply: We thank Eleftheriadis *et al.*[1] for their interest in our work.[2] We believe that our observations regarding the confounding effect of pre-existing protein–energy wasting on the associations of ghrelin with inflammation, leptin, and outcome[2] help to reconcile apparent discrepancies between epidemiological[3] and interventional studies[4] on the existence of a resistance to the action of ghrelin in chronic kidney disease. Their report that there is no difference in acylated ghrelin between healthy volunteers and hemodialysis patients, but reduced acylated ghrelin in patients with cardiovascular disease, may as well represent, as they indicate, the epiphenomenon of concurrent cachexia. The inability of observational studies to denote causality in these associations warrants altogether the need to delve deeper into the effects of ghrelin administration in the outcome of dialysis patients. Ghrelin is truly an exciting therapeutic agent with a range of purported beneficial effects not only on anorexia but also on inflammation and the cardiac system, and new treatment strategies to tackle the excess mortality of this patient group are urgently needed. However, we still have some questions to address: although animal studies suggest that acylated ghrelin stimulates appetite, Barazzoni *et al.*[5] postulated that relative acylated ghrelin excess could contribute to obesity-associated insulin resistance in metabolic syndrome. The risks of developing ghrelin resistance, its mitogenic potential, and the costs for ghrelin treatment also need consideration.[6] Although a small-scale clinical trial[4] has provided encouraging evidence on the short-term orexigenic effects of subcutaneous acylated ghrelin administration (1 week) in malnourished dialysis patients, we need still to proceed cautiously until these concerns are clarified.

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