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Is ghrelin a biomarker for mortality in end-stage renal disease?

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Ghrelin is involved in the pathogenesis of protein-energy wasting (PEW), inflammation, and cardiovascular complications in end-stage renal disease (ESRD). Plasma ghrelin may prove to be a powerful biomarker of mortality in ESRD but should be considered in the context of assay specificity, other weight-regulating hormones, nutritional status, systemic inflammation, and cardiovascular risk factors. ESRD patients with PEW, systemic inflammation, and low ghrelin and high leptin concentrations have the highest mortality risk and may benefit the most from ghrelin therapy.

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Survival with end-stage renal disease (ESRD) is worse than with most cancers. The mortality rate of maintenance dialysis patients is above 20% per year, with more than half of the deaths related to cardiovascular complications.[1] A large number of biomarkers for mortality in ESRD have been published and include those associated with traditional cardiovascular risk factors, inflammation, and protein-energy wasting (PEW).[2] Ghrelin is involved in the pathogenesis of all three of these pathways and may therefore be a very powerful biomarker for survival outcomes in patients with ESRD (Figure 1). Carrero and colleagues[3] (this issue) report that ESRD patients with inflammation-associated PEW and low ghrelin and high leptin concentrations have the highest mortality risk.

Three distinct ghrelin gene products, namely, acyl ghrelin, des-acyl ghrelin, and obestatin, have been identified. Acyl ghrelin is the endogenous cognate ligand for growth hormone secretagogue receptor 1a (GHS-R1a) and constitutes only 10% of the circulating hormone. Des-acyl ghrelin, the non-acylated form, from alternative splicing of the ghrelin gene, is the major molecular form in the circulation. Ghrelin *O*-acyltransferase (GOAT), which acylates ghrelin at the serine-3 position, is an important enzyme that controls the conversion of des-acyl to acyl ghrelin. The third ghrelin gene product, obestatin, is derived from the mammalian prepro-ghrelin gene by comparative genomic analysis. Acyl ghrelin is a circulating hunger hormone and is considered the counterregulatory hormone for leptin. Des-acyl ghrelin has also been shown to actively participate in food intake. Des-acyl ghrelin is secreted in a highly regulated manner in response to food deprivation in mice. Intracerebroventricular administration of rat des-acyl ghrelin to rats or mice stimulates feeding, but peripheral administration has no effect. Obestatin binds to an orphan G protein-coupled receptor, GPR39, to inhibit food intake by activating anorexigenic neurons in several brain regions. Thus, acyl ghrelin has orexigenic and des-acyl ghrelin and obestatin have anorexigenic effects. It is important to assess the contribution of these different counterregulatory circulating ghrelin proteins as well as leptin in the consideration of weight regulation disorders.[4]

The kidney degrades ghrelin. Increased total plasma ghrelin levels in ESRD are primarily due to the decreased degradation of ghrelin in the kidney. Studies of circulating ghrelin in patients with ESRD have yielded inconsistent findings due to several confounding factors. The traditional radioimmunoassay method measures the sum of both acylated and des-acyl ghrelin. More specific assays show that only plasma des-acyl ghrelin levels were elevated in ESRD patients.[5] Most studies do not account for obestatin. Likewise, the study of Carrero and colleagues[3] only measures total ghrelin by the traditional radioimmunoassay, and therefore its results have to be interpreted with these limitations in mind. Furthermore, it is important to assess ghrelin in the context of the nutritional status, since ghrelin participates in weight and body composition regulation. Total skeletal muscle mass is a negative predictor of plasma ghrelin concentrations. Administration of a ghrelin mimetic significantly increases fat-free mass. Elevated plasma ghrelin also correlates with fat mass in ESRD patients.[4] Thus, one would expect plasma acyl ghrelin, an orexigen and positive regulator of body and muscle mass, to be upregulated in anorexic and wasting conditions. PEW is prevalent in ESRD patients, and presence of normal to high plasma acyl ghrelin concentrations may represent ghrelin resistance, which could be due to elevated anorexigenic hormones such as leptin in the circulation. In this respect, the study by Carrero *et al.*[3] provides important and novel information. The phenotype of PEW and high leptin and low ghrelin concentrations would represent a failure of ghrelin secretion to provide compensatory counterregulation, much like in the advanced type 2 diabetic patient with insulin resistance and decreased insulin secretion culminating in frank diabetes.

Ghrelin has significant anti-inflammatory effects. Treatment of rats after subtotal nephrectomy reverses uremic cachexia

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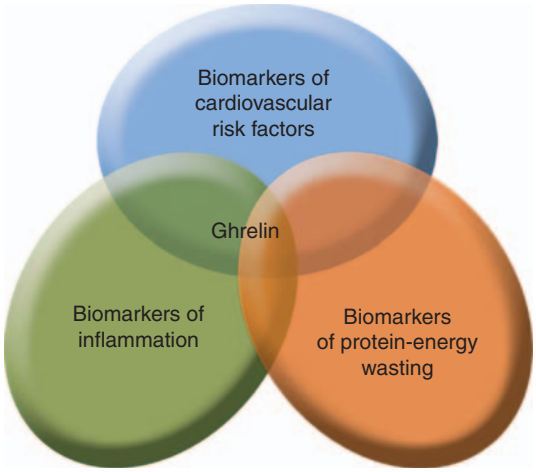

Figure 1 | Ghrelin is a common factor in three different biomarker pathways that are associated with increased mortality in end-stage renal disease.

and, at the same time, causes a decrease in circulating inflammatory cytokines, such as tumor necrosis factor and interleukin-6. Ghrelin-treated uremic animals also had a decrease in the expression of the interleukin-1 receptor in the brainstem.[6] On the other hand, systemic inflammation modulates ghrelin levels. Ghrelin levels fall in states of acute inflammation such as bacterial lipopolysaccharide-induced cachexia, and the mechanism may involve the interleukin-1β receptor. Mice with genetic deletion of the interleukin-1β receptor do not suppress circulating ghrelin levels with lipopolysaccharide administration. Ghrelin concentrations are initially suppressed in experimental arthritis as well as in patients with rheumatoid arthritis. This is followed by recovery of ghrelin concentrations, representing a compensatory mechanism to cachectic conditions. Thus it is important to assess the presence of systemic inflammation when considering serum ghrelin as a biomarker of mortality in ESRD. Indeed, chronic inflammation may have a stronger causal role in engendering atherosclerotic cardiovascular disease than traditional risk factors such as low-density lipoprotein hypercholesterolemia in ESRD.

Ghrelin receptors are widely expressed in the cardiovascular system. Ghrelin has beneficial effects in various cardiovascular disease states.[7] Ghrelin improves cardiac contractility, reduces myocardial infarct size, and attenuates the reduction in left ventricular function induced by experimental cardiac ischemia–reperfusion. Ghrelin has been shown to increase body weight, cardiac output, and diastolic thickness of the noninfarcted posterior wall, as well as to inhibit left ventricular enlargement. In animal models of heart failure, ghrelin administration improves cardiac contractility and attenuates the development of cardiac cachexia.[8] In normal subjects, intravenous or subcutaneous ghrelin injection increases cardiac output, improves cardiac contractility, and causes a significant decrease in mean arterial pressure. Ghrelin has a therapeutic effect in patients with heart failure. It improves left ventricular function, attenuates left ventricular and decreases systemic vascular resistances, and increases cardiac output, cardiac index, and stroke volume index in patients with chronic heart failure. Ghrelin also increases body weight, lean body mass, and muscle strength in these patients.[9] These results suggest that ghrelin could improve muscle wasting in patients with chronic heart failure and cardiac cachexia, a severe catabolic state similar to PEW in ESRD and resistant to long-term treatment with nutritional supplements. In keeping with these findings, other studies have emphasized that ghrelin might have a role in patients with end-stage heart failure and cardiac cachexia, by improving cardiac function and increasing appetite. Intravenous administration of ghrelin has therefore been proposed as adjuvant therapy in heart failure, because of its beneficial effects on left ventricular mass, left ventricular ejection fraction, and left ventricular end-systolic volume.[9] Ghrelin may also have a beneficial effect on hypertension. A negative correlation has been noticed between ghrelin plasma levels and blood pressure. Ghrelin suppresses sympathetic activity and decreases blood pressure through mechanisms involving the central nervous system and sympathetic regulation. Ghrelin administration significantly decreases plasma norepinephrine levels and the ratio of low- to high-frequency spectra of heart rate variability in rats with myocardial infarction. Ghrelin infusion reduces peripheral resistance and blood pressure levels in humans, even though supraphysiological hormone levels are required to produce this effect. Ghrelin may also reduce blood pressure by vasodilation via effects on the endothelium and/or vascular smooth muscle cells.[7] Thus, ghrelin may have multiple beneficial effects on the cardiovascular complications in ESRD. Assessment of cardiovascular risk factors such as blood pressure and left ventricular mass and function as well as indices of congestive heart failure would have been very helpful in this consideration but was unfortunately not available in the study by Carrero *et al.*[3]

In summary, ghrelin has significant regulatory roles in energy homeostasis, systemic inflammation, and the cardiovascular system. Thus, ghrelin is important in the pathogenesis of PEW, systemic inflammation, and cardiovascular complications in ESRD, all of which are significantly associated with patient outcomes, including mortality. Plasma ghrelin may prove to be a powerful biomarker of mortality in ESRD but should be best considered in the context of assay specificity, other weight-regulating hormones, nutritional status, systemic inflammation, and cardiovascular risk factors. Ghrelin and its analogs have shown promise in improving anorexia in short-term studies in ESRD patients. The clinical utility of ghrelin will depend on long-term outcomes in reversing PEW as well as improving morbidity and mortality.[10] ESRD patients with PEW, systemic inflammation, and low ghrelin and high leptin concentrations have the highest mortality risk and may benefit the most from ghrelin therapy.

DISCLOSURE
The authors declared no competing interests.

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ANCA comes of age—but with caveats

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Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis are predominantly diseases of older patients, frequently involving the kidney. Bomback and colleagues studied disease outcome in very elderly patients (>80 years old) with ANCA-associated renal disease. Immunosuppression resulted in lower rates of end-stage renal disease at 1 year and lower mortality at 2 years. Although these data suggest we should treat these elderly patients with immunosuppression, the criteria for patient selection and the dosage and duration of the treatment regimen need to be established.

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Anti-neutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitides are predominantly diseases of older patients, frequently involving the kidney with focal necrotizing glomerulonephritis, and resulting in significant morbidity and mortality. The majority of clinical trials investigating therapeutic regimens have recruited patients between 18 and 75 years old, leaving uncertainty regarding treatment outcomes in those older patients for whom the risks of immunosuppressive treatment are frequently perceived to outweigh the benefits. Bomback and colleagues[1] (this issue) have performed a study to address disease outcome specifically in very elderly patients (>80 years old) with ANCA-associated renal disease. They report that immunosuppression resulted in lower rates of end-stage renal disease (ESRD) at 1 year and lower mortality at 2 years. So, on the basis of these data, should we be treating all our vasculitic patients with the same immunosuppressive protocols regardless of their age?

ANCA-associated vasculitis (AAV) constitutes a heterogeneous group of disorders with an incidence of around 20 per million per year and a peak age of 65–74 years.[2] In the elderly, AAV may present atypically or with vague constitutional symptoms and can thus be difficult to diagnose. A high index of clinical suspicion is required, evidenced by the fact that ANCA-associated pauci-immune glomerulonephritis is the most common finding in very elderly patients biopsied for acute kidney injury.[3] AAV may be life-threatening, and, before the introduction of immunosuppressive treatment, mortality was as high as 85% at 1 year; this was radically transformed with the use of corticosteroids and alkylating agents.[4] Even with modern treatment protocols, AAV results in considerable morbidity, with end-stage renal failure developing in 20–30% of patients at 5 years, and significant mortality, with 18 and 24% of patients dead by 1 and 5 years, respectively.[5] Treatment is generally divided into more intensive induction therapy followed by long-term maintenance treatment, but despite this, relapse rates are high, reaching almost 50% over 5 years.[6]

Treatment with immunosuppressive agents, such as cyclophosphamide and steroids, is associated with considerable side effects and cumulative toxicity, and a quarter of patients develop an adverse reaction during the first year of treatment.[4] Little *et al.*[7] have successfully teased out the relative importance of disease activity and treatment-related complications in contributing to early patient death. Prospective data from four European Vasculitis Study Group trials were used to compare the effects of vasculitis activity and adverse events on early mortality in 524 patients. One-year mortality probability was 11.1%, with 59% of deaths attributable to adverse events

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