Obestatin, a Ghrelin-Cognate Protein, and Clinical Outcomes in Hemodialysis Patients

Carmine Zoccali^a Francesca Mallamaci^{a, b}

^aCNR-IFC, Clinical Epidemiology and Pathophysiology of Hypertension and Renal Diseases, Reggio Calabria, Italy;

^bNephrology, Hypertension and Renal Transplantation Unit, Ospedali Riuniti Reggio Calabria, Reggio Calabria, Italy

The discovery of the gastrointestinal hormone ghrelin, a 28-aminoacids orexigenic peptide, is considered as one of the most important advancements in the last 2 decades for our understanding of physiological mechanisms regulating hunger and food intake. This peptide interferes with the hypothalamic melanocortinergetic system and is endowed with pleiotropic metabolic effects. Ghrelin stimulates the growth hormone secretagogue receptor – a G protein-coupled receptor highly expressed in the pituitary gland as well as in various brain areas, in the thyroid and in the pancreas – which activates orexigenic neural networks in the hypothalamus and stimulates food intake-independent lipogenesis, thereby increasing fat mass and body weight. Beyond its orexigenic effect, ghrelin also regulates taste, gut motility, glucose metabolism, and the sleep-wake rhythm.

Obestatin is an emerging anorexigenic peptide closely related to ghrelin which derives from alternative splicing of the same precursor molecule, preproghrelin. In humans, obestatin is mainly localized to the gastrointestinal tract, particularly in the stomach. This compound may reduce food intake and gastric emptying but these effects are still not firmly established [1]. On the other hand, it is fairly well demonstrated that obestatin increases glucose

uptake and insulin sensitivity and inhibits lipolysis and may have a favorable impact upon the vascular system and the heart [2, 3]. Because of these metabolic and cardiovascular effects, obestatin is considered as an interesting target for cardiovascular disease prevention in human obesity and in diabetes. In line with this possibility, the infusion of increasing doses of this peptide in lean and obese subjects [4] induces a nitric oxide-mediated progressive rise in forearm blood flow. The potential relevance of obestatin in cardiovascular disease is also suggested by the fact that circulating levels of this compound are raised in subjects with essential hypertension and in pregnancy-related hypertension as well as in heart failure, particularly in patients with heart failure and cachexia [3].

End stage kidney disease (ESKD) is a condition where protein energy wasting, insulin resistance, inflammation, and anorexia are very frequent. These alterations signal a high risk for death and cardiovascular disease, and are considered to be a dominant factor in the dim prognosis of ESKD patients. Of interest, the relationship between protein energy wasting (PEW) and mortality is particularly high when PEW is associated with inflammation because the risk of death in wasted and inflamed patients is

more than additive as compared to that in patients who show PEW alone or inflammation alone [5]. The pathogenesis of PEW in ESKD is multifactorial in nature and infection; comorbidities (diabetes and cardiovascular disease), secondary hyperparathyroidism, growth hormone resistance, insulin resistance, hypogonadism, and depression are all implicated into this syndrome.

Anorexia is a hallmark of PEW and accumulation of anorexigenic peptides like leptin or cytokines, namely interleukin (IL)-6 and tumor necrosis factor- α , have been suspected to be responsible for the lack of appetite in ESKD patients with PEW. Ghrelin, a hormone that increases appetite, attains high levels in ESKD and such a rise probably serves to mitigate anorexia because the plasma concentration of this peptide is directly related to body fat in this condition. Obestatin, a putatively anorexigenic peptide with cardiovascular protective effects, is an interesting factor to fit into the complex pathophysiological scenario of the PEW inflammation syndrome of ESKD patients. However, until now, there has been very limited interest on obestatin in ESKD patients. In 2013, Beberashvili et al. [6], the same authors of an article published in this issue of the Journal that we will comment later on [7], reported that high obestatin entails an excess risk for low energy intake and associates with higher fat mass which is an effect opposite to that one would expect from an anorexigenic hormone. Such an observation is in keeping with experimental data in animal models negating an anorexigenic effect by obestatin [1] but is in sharp contrast with findings in diabetes and in obesity linking these conditions with low obestatin levels [3]. In their 2013 study, Beberashvili et al. [6] also observed that low obestatin predicts a high death risk, which is in line with the hypothesis that this peptide may represent a cardiovascular protective hormone.

Even though intriguing and hypothesis-generating, this cohort study was inherently limited by the dimension of the study cohort (just 94 patients) and the small number of clinical events (just 39 deaths, 15 due cardiovascular disease). A general caveat in observational studies in ESKD is that high levels of uremic solutes may signal a high death risk even when the same solutes have no real biological interference with the pathomechanism(s) that may influence human health. Such a confounding is due to the fact that the accumulation of these solutes in part reflects the severity of the uremic syndrome or alterations triggered by ESKD rather than noxious pathomechanisms. This is, for example, the case of brain natriuretic peptide, a cardioprotective protein synthesized mainly in the heart (thereby reflecting alterations in left ventricular

mass and function), which is a direct predictor of the risk of death in this population. However, for uremic solutes that are inversely – rather directly – related with death or cardiovascular disease in ESKD, the problem of confounding by accumulation attributable to kidney failure poses less interpretative problems. This is the case of some biomarkers endowed with putatively cardioprotective action like the soluble receptor of advanced glycosylation end products or adiponectin (at least in some studies). In such cases, appropriately adjusted analyses may produce results reliably reflecting the underlying biological role of the same biomarkers.

In the study published in this issue of the Journal [7], Beberashvili et al. [6] present new analyses on the relationship between obestatin and the risk of all-cause and cardiovascular deaths in ESKD. The study cohort is now larger (261 patients) and the number of events registered over a 39-month follow-up was substantially higher (160 deaths, with 74 deaths due to cardiovascular disease) than that of the previous study. Interestingly, the new analyses confirm the inverse association between circulating obestatin and all-cause and cardiovascular mortality registered in the first study [6]. However, the risk reduction portended by higher (1 ng/mL, a concentration about one-third of the average value in healthy subjects) obestatin is relatively small (–10 and –15% for all-cause and cardiovascular deaths) in analyses adjusted for other risk factors including parameters of nutritional status, inflammation biomarkers like IL-6, the 2 main adipokines (leptin and adiponectin), and the cognate orexigenic peptide ghrelin. Nonetheless, such an apparently modest effect should be considered of relevance for 2 reasons. First, the high mortality risk of ESRD is multifactorial in nature and therefore single risk factors per se are much unlikely to explain a high proportion of the death risk in this population. Second, because some major risk factors included into the multivariable analysis, like nutritional status parameters – rather than confounders – may well represent intermediate mechanisms whereby obestatin eventually triggers all-cause and cardiovascular deaths. Of interest, the risk by low obestatin was amplified in older patients, a category with a higher cardiovascular burden and shorter life expectancy, and in patients with high IL-6, the most powerful inflammation biomarker in ESKD. Other apparently synergistic effects between obestatin and tumor necrosis factor- α or ghrelin described in the same study are difficult to interpret because the lack of a clear biological underpinning and the large series of tested interactions, which may produce false positive findings.

Overall, the cohort study by Beberashvili et al. [6] apparently supports the hypothesis that obestatin is an additional, potentially relevant player in the high risk of death and cardiovascular complications in ESKD. Mechanistic studies and confirmation of findings in other large ESKD cohorts are now needed to advance our knowledge on the relationship between this intriguing peptide and health outcomes in ESKD. The issue is important because obestatin can have a favorable impact upon endothelial dysfunction and insulin resistance, which are almost universal alterations in ESKD. A pilot clinical trial has shown that ghrelin – the peptide structurally related with obestatin and interacting with this peptide in determining several metabolic functions – improves the appetite

and induces a positive energy balance in ESKD patients [8]. In the face of a strong interest on adipose tissue cytokines like leptin and adiponectin, clinician investigators with an interest on renal nutrition and cardiovascular risk until now have almost ignored obestatin. Given the promising findings in the cohort study by Beberashvili et al. [7], focusing on obestatin appears to be a worthwhile and perhaps rewarding research effort for investigators in the field.

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References

- 1 Gourcerol R: Obestatin; in Kastins AJ (ed): *Handbook of Biologically Active Peptides*, ed II. Elsevier Inc., 2013, pp 1275–1282.
- 2 Cowan E, Burch KJ, Green BD, Grieve DJ: Obestatin as a key regulator of metabolism and cardiovascular function with emerging therapeutic potential for diabetes. *Br J Pharmacol* 2016;2165–2181.
- 3 Ku JM, Andrews ZB, Barsby T, Reichenbach A, Lemus MB, Drummond GR, et al: Ghrelin-related peptides exert protective effects in the cerebral circulation of male mice through a nonclassical ghrelin receptor(s). *Endocrinology* 2015;156:280–290.
- 4 Schinzari F, Veneziani A, Mores N, Barini A, Di Daniele N, Cardillo C, et al: Vascular effects of obestatin in lean and obese subjects. *Diabetes* 2017;66:1214–1221.
- 5 de Mutsert R, Grootendorst DC, Axelsson J, Boeschoten EW, Krediet RT, Dekker FW, et al: Excess mortality due to interaction between protein-energy wasting, inflammation and cardiovascular disease in chronic dialysis patients. *Nephrol Dial Transplant* 2008;23:2957–2964.
- 6 Beberashvili I, Sinuani I, Azar A, Kadoshi H, Shapiro G, Feldman L, et al: Low serum concentration of obestatin as a predictor of mortality in maintenance hemodialysis patients. *Biomed Res Int* 2013;2013:796586.
- 7 Beberashvili I, Katkov A, Sinuani I, Azar A, Shapiro G, Feldman L, Gorelik O, Stav SEK: Serum obestatin: a biomarker of cardiovascular and all-cause mortality in hemodialysis patients. *Am J Nephrol* 2018;47:254–265.
- 8 Wynne K, Giannitsopoulou K, Small CJ, Patterson M, Frost G, Ghatei MA, et al: Subcutaneous ghrelin enhances acute food intake in malnourished patients who receive maintenance peritoneal dialysis: a randomized, placebo-controlled trial. *J Am Soc Nephrol* 2005;16:2111–2118.