In search of acute surgical stress biomarkers: Is ghrelin a potential candidate?

Sir,

Ghrelin, a 28-amino-acid peptide, is the endogenous ligand for the growth hormone (GH) secretagogue receptor and its discovery has led to a more thorough understanding of the close interplay between energy balance, regulation of appetite, and gastrointestinal functionality.[1,2] Mainly secreted by gastric cells, ghrelin has traditionally been associated with the stimulation of appetite and increase of food intake as well as with the stimulation of GH secretion and the exhibition of a prokinetic effect upon the upper gastrointestinal (UGI) tract.[3,4] However, there is an explosive amount of clinical and laboratory studies, suggesting that ghrelin demonstrates significant anti-inflammatory actions, with these observations being attributed to the ability of ghrelin to suppress the production of proinflammatory cytokines, including interleukins (IL-1 β, IL-6), and tumor necrosis factor alpha (TNF-α).[5,6] Moreover, ghrelin has also been shown to promote lymphocyte development in the primary lymphoid organs (bone marrow and thymus) and to ablate age-associated thymic involution.[7] Ghrelin exerts its potent inhibitory effect by reducing messenger ribonucleic acid (mRNA) and protein expression through the GH secretagogue receptor and inhibits anti-cluster of differentiation 3 (CD3)-activated murine T-cells in a dose-dependent manner and it also appears to affect the production of Th1 and Th2 cells in a non-specific manner.[8]

Extensively studied in patients with suffering from cardiometabolic diseases and nutritional disorders,[9] until recently, the role of evaluation of ghrelin levels in surgical patients has predominantly been restricted in UGI surgery, mainly in order to assess the hormonal effects of the various types of obesity surgery as well as a marker to detect appetite disorders and risk for cachexia after oncological operations.[10,11] However, since the UGI system appears to be simultaneously the main source and main target of ghrelin, it would be rather endangered to suggest that possible perioperative fluctuations of ghrelin levels in UGI surgery could accurately reflect the extent of acute surgical stress. From this point of view, we performed a review of the current literature in search of clinical studies that examine the potential significance of measuring ghrelin as a biomarker of acute surgical stress in non-UGI surgical patients, realizing that the relevant published data are extremely scarce.

In the most recently published study, Kontoravdis *et al*.[12] evaluated the effect of acute surgical stress on ghrelin serum levels, enrolling in their prospective study two groups of patients, scheduled to undergo elective colectomy or cholecystectomy. The authors reported that in both groups serum ghrelin concentrations reached their peak level at 24 h post-operatively, being significantly higher compared to the pre-operative ones. Serum ghrelin values returned to the pre-operatively measured levels by the 48 h post-operatively while patients' gender, age, American Society of Anesthesiologists (ASA) score and type of surgical procedure (colectomy or cholecystectomy) did not influence the serum ghrelin levels. In accordance with the above mentioned are the results of a similar study, which compared the perioperative fluctuations of serum ghrelin levels in patients who were submitted to colectomy and cholecystectomy, by Maruna *et al*.,[13] who observed a significant elevation of plasma ghrelin levels 24 h after resection of coli and subsequent return to baseline measurements 36-48 h after surgery. However, in this study, patients who were submitted to colectomy had significantly higher post-operative values of ghrelin compared to the cholecystectomized patients.

In another study, Chiesa *et al*.[14] investigated the existence of any alterations in serum ghrelin levels during the performance of elective cholecystectomy, categorizing their study sample according to the adoption of an open or laparoscopic approach. Interestingly, their findings were suggestive of a significant decrease of ghrelin concentrations from baseline during the intraoperative period for all patients undergoing elective cholecystectomy; however, failing to demonstrate any approach-dependent differences of serum ghrelin values. Similar results were reported by Cetinkaya *et al*.[15] in a study, they conducted in order to determine the possible differences between the serum and saliva ghrelin concentrations before and after surgery in patients submitted to appendectomy and elective cholecystectomy. The researchers failed to show any differences in ghrelin levels in patients undergoing laparoscopic cholecystectomy, but did show an increase in the hormone levels in patients undergoing appendectomy.

Even in the framework of these preliminary clinical studies, it appears that ghrelin levels could be of potential value as biomarker of acute surgical stress. The

controversial results of the current data could reasonably attributed to the low statistical power of the involved studies, the vast heterogeneity concerning the pre-analytical and analytical phases of the laboratory measurements of ghrelin levels as well as significant differences between the enrolled patients in terms nutritional status and cardio-metabolic comorbidities. The clarification of the role of ghrelin in the mechanisms regulating the immunoregulatory response toward surgical stress, especially when sepsis occurs, is of paramount importance concerning its potential use as a biomarker or as a therapeutic agent. Since surgery is often performed in patients with (early) sepsis, it is rather endangered to attempt to attribute the post-operative fluctuations of ghrelin only to the presence of one of the two factors, surgery or sepsis, fact that highlights the need for further experimental and clinical studies with well-defined aims and parameters. The elucidation of the pathophysiological mechanisms that regulate the endocrine response to acute surgical stress is of paramount importance in the future of surgery as it will enable the surgeon to quantify the "stress load" of the various surgical approaches, tailored to the patient's baseline nutritional condition, cardio-metabolic function and underlying acute or chronic surgical pathology. Although limited, the current data seem to favor that ghrelin has a role to play as a marker of acute surgical stress and lead the way for the establishment of a truly rounded approach to the surgical patient.

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