



Weighing in on Ghrelin and the Preservation of Muscle After Esophagectomy

Evan T. Alicuben, MD¹, and Anthony W. Kim, MD²

¹Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA; ²Division of Thoracic Surgery, Department of Surgery, Keck School of Medicine, University of Southern California, Los Angeles, CA

Although technical advances paired with increasingly sophisticated postoperative care have successfully reduced the mortality after esophagectomy, the morbidity associated with this complex and nuanced operation remains high.¹ Central to understanding and making meaningful headway on an operation demanding to the surgeon and markedly taxing to the patient is mitigating the loss of muscle mass, an independent factor in overall prognosis, which some have used as a preoperative predictor for outcomes.^{2,3}

Although the conventional philosophy of aggressive nutritional supplementation and early mobilization remain as fundamental underpinnings of perioperative success, there most assuredly are either undiscovered or only preliminarily explored adjunctive measures that can augment the intended effect of this traditional thinking. In this issue of *Annals of Surgical Oncology*, Nose et al.⁴ publish their thought-provoking results showing the effects of postoperative ghrelin administration on skeletal muscle loss after esophagectomy.

Patients who underwent esophagectomy for cancer were randomized to receive a continuous infusion of ghrelin at a high dose, infusion of ghrelin at a low dose, or placebo for 7 days after surgery. Two important differences were detected between the groups. First, the patients receiving high-dose ghrelin had significantly less weight loss at 7 days than those receiving a placebo. In fact, the patients

who received high-dose ghrelin had an increase in weight at that time point. Furthermore, when erector spinae muscle mass was used as a marker to predict sarcopenia, the rate of muscle loss for both the high- and low-dose ghrelin groups was lower than for the placebo group.

Second, important differences in serum markers and hormone levels were elucidated between the groups. Transferrin, relevant for monitoring nutritional status, measured on postoperative day 14, was significantly higher in the patients receiving ghrelin than in the placebo group. Interestingly, the levels of both growth hormone and insulin-like growth factor-1 were higher in the high-dose group than in the placebo group, which given their role in muscle metabolism hints at a likely mechanism for the slowed muscle loss observed.

These findings begin to unveil the possibilities of using adjunctive measures to optimize patient metabolism during the critical perioperative period. However, it is notable that although the difference in rate of erector spinae muscle mass loss persisted for the high-dose ghrelin group, the initial difference in overall weight loss disappeared by day 30. Similarly, although the difference in serum insulin-like growth factor-1 level remained significant, the growth hormone levels became similar at 14 days. Additionally, there were no differences in the most used markers of nutrition: prealbumin, albumin or protein levels. Although this finding may be disappointing, it is critical to note the dose-response relationship seen between low- and high-dose ghrelin groups. Further titration of the dose, duration, and frequency of ghrelin administration likely will lead to significant and persistent differences.

Coupled with the authors' original study that administered ghrelin, it appears that both the timing and duration of this intervention may be the next natural areas to evaluate. These added dimensions of timing and duration of ghrelin

administration are critical to understanding the long-term effects in terms of attenuating muscle loss. As many surgeons worldwide can attest, postoperative and surveillance visits typically include more coarse assessments of nutrition through measurements of weight and body mass index. Some evaluations may include the classic nutritional markers the authors included in their study. However, the other markers currently are not routinely evaluated due to the lack of data implicating their utility.

Although laboratory studies of factors such as ghrelin, growth hormone, and insulin-like growth factor-1 may be ordered in the future, the current study highlights the need to establish an association between the administration of ghrelin and longer-term outcomes. It will not be surprising if the administration of ghrelin emerges as a key adjunctive intervention to ensure a smoother peri- and postoperative course. Until then, questions regarding the potential deleterious effects of other anabolic agents such as growth hormone and insulin-like growth factor-1 in the context of more advanced or occult disease require fleshing out to a greater extent. Given that neoadjuvant systemic therapy regimens have become widely accepted for most stages of resectable esophageal cancer, the effects of ghrelin administration in the setting of in situ disease among these patients especially at risk for significant loss of muscle mass could prove to be golden information. As with all issues that pertain to life, the balance between administering a new agent must be weighed against the trade-offs to its administration.

Within the challenging perioperative period after esophagectomy, a preservation of muscle mass may bring about greater resistance especially to respiratory complications, quicker improvement in functional status, and an expedited return to baseline, which should be the ultimate goal for most patients. This would have important implications for patients needing adjuvant systemic therapy. If ghrelin effectively mitigates muscle mass loss and thereby increases the likelihood of a full recovery, then perhaps these patients will be more likely to receive adjuvant therapy successfully. Ultimately, this logic could translate into achieving the primary goal of improved survival when esophageal cancer patients are surgically managed with a curative-intent treatment. Therefore, although this study did not detect a difference in perioperative complications or longer-term outcomes, an underappreciated facet of this study may have included a subset of patients who actually

benefited from the administration of postoperative ghrelin and who otherwise would have failed to thrive. The lack of observed difference in perioperative complications and longer-term outcomes may have been driven by averting adverse outcomes in the short term due to the benefits of postoperative ghrelin.

Ultimately, this specific study by Nose et al. represents yet another notch in the proverbial ever-expanding ghrelin belt of knowledge, clearly an area in which the authors have delineated themselves as experts. They continue to expand the muscular belly of surgical knowledge implicating ghrelin administration as benefiting those undergoing esophagectomies while whetting the appetite of countless surgeons craving improved outcomes. Their effort in both their previous work and this study has been foundational for future studies performed to examine the innumerable downstream metabolic effects associated with ghrelin administration. Perhaps the observations from this study represent the first step in shifting the paradigm from putting meat back on the bones of patients to preventing them from losing it in the first place.

DECLARATIONS

DISCLOSURES There are no conflicts of interest

REFERENCES

1. Wang H, Tang H, Fang Y, et al. Morbidity and mortality of patients who underwent minimally invasive esophagectomy after neoadjuvant chemoradiotherapy vs neoadjuvant chemotherapy for locally advanced esophageal squamous cell carcinoma: a randomized clinical trial. *JAMA Surg.* 2021;156:444–51.
2. Maeda N, Shirakawa Y, Tanabe S, Sakurama K, Noma K, Fujiwara T. Skeletal muscle loss in the postoperative acute phase after esophageal cancer surgery as a new prognostic factor. *World J Surg Oncol.* 2020;18:143.
3. Tang A, Ahmad U, Raja S, et al. Looking beyond the eyeball test: a novel vitality index to predict recovery after esophagectomy. *J Thorac Cardiovasc Surg.* 2021;161:822–32 e826.
4. Nose Y, Yamashita K, Takeoka T, et al. Perioperative ghrelin administration attenuates postoperative skeletal muscle loss in patients undergoing esophagectomy for esophageal cancer: secondary analysis of a randomized controlled trial. *Ann Surg Oncol.* 2022. <https://doi.org/10.1245/s10434-022-11436-0>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.