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Review

Cancer Cachexia: The Comparative Mechanisms of Weight Loss after Esophagectomy and Bariatric Surgery

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Abstract

Oesophageal cancer is the ninth most common cancer and the sixth most common cause of cancer deaths worldwide [1]. Over the past number of years, due to earlier diagnosis and better treatment, we are seeing improvements in the survival rates of oesophageal cancer, with more patients living longer post-esophagectomy surgery. Unintentional weight loss is a common unintended feature seen in patients post-esophagectomy done with curative intent. Many recent studies have demonstrated the links between the pathophysiology of the weight loss following esophagogastric cancer surgery and the biological mechanism of weight loss following bariatric surgery. The predominant cause of the weight loss in both circumstances appears to the postoperative alterations in gut hormone signalling. This paper explores these over-lapping gut hormones signalling mechanisms and discusses the use of this increased understanding of hormone signalling to develop potential pharmacologic targets for the management of unintentional weight loss post-esophagogastric cancer surgery.

Keywords

Cancer cachexia; weight loss; esophagectomy; bariatric surgery

1. Introduction

Oesophageal cancer is the ninth most common cancer and the sixth most common cause of cancer deaths worldwide [1]. Over the past number of years, due to earlier diagnosis and better treatment, we are seeing improvements in the survival rates of oesophageal cancer, with more patients living longer post-esophagectomy surgery. This has brought the long-term complications of oesophagectomy into clinical focus, especially that of unintentional weight loss, which is defined as >5 % of body weight loss within 6-12 months. Bariatric surgery is one of the most effective therapeutic interventions for metabolic diseases [2]. The weight loss seen in patients post-oesphagectomy has helped us to understand the mechanisms by which bariatric surgery may affect energy homeostasis in overweight and obese populations, with gut hormones playing a pivotal role [3, 4]. Recent studies have looked at cancer cachexia, its mechanisms and potential treatments [5, 6]. While cancer cachexia may be a cause of unintentional weight loss in patients who are not in remission of oesophageal cancer, the main focus of this article is on patients who are in remission of oesophageal cancer. In these patients, the critical factors driving the unintentional weight loss post-oesphagectomy lie primarily in endocrine mechanisms and changes to the gut-brain pathway caused by surgery. This paper explores these over-lapping gut hormones signalling mechanisms and discusses the use of this increased understanding of hormone signalling to develop potential pharmacologic targets for the management of unintentional weight loss post-esophagogastric cancer surgery.

2. Oesophagectomy to Cure Oesophageal Cancer

Oesophageal cancer accounts for 27,700 deaths per year in the European Union [7]. Oesophagectomy is a major resection of the oesophagus and stomach and is part of the multimodal (adjuvant chemo[radio]therapy) treatment [8] (See Figure 1). Initially after surgery, patients may require additional chemo(radio)therapy and feeding jejunostomy [9]. Almost 40-50% of patients remain cancer free 5 years after oesophagectomy [10, 11]. However, more than half of them have unintentional weight loss as they involuntarily reduce their food intake [12].

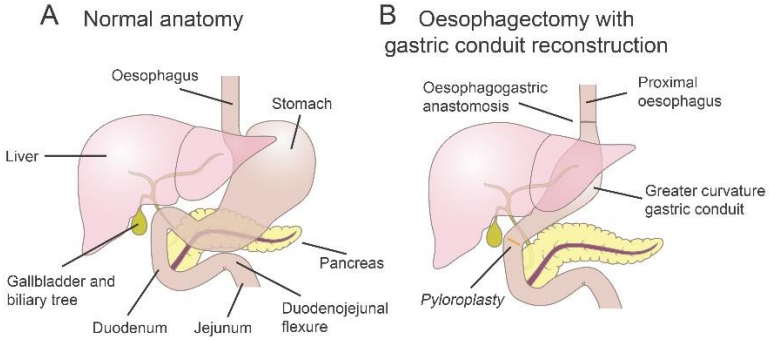

Figure 1 A. Normal anatomy and B. oesophagectomy with gastric conduit reconstruction, with or without pyloroplasty resulting in rapid nutrient transfer to the small bowel [13, 14].

Prior to curative surgery for cancer, unintentional weight loss is common and secondary to anorexia, dysphagia, and cancer cachexia [15]. Initially after curative surgery, the surgical stress [16] and mucositis during chemo(radio)therapy further reduces food intake [17]. In contrast with comparable operations, restoration of normal food intake and weight gain does not typically occur after oesophagectomy [18]. Weight loss after surgery increases long term morbidity and mortality even when cancer is cured [19-23] and cannot be attributed to cancer cachexia, unless there is a recurrence of the cancer. Nutritional support improves morbidity, but not oncologic outcomes [24], while patients cannot voluntarily increase food intake after oesophagectomy [12]. The severity of pancreatic exocrine insufficiency, bacterial overgrowth and/or dumping syndrome does not correlate with unintentional weight loss and appropriate treatments do not consistently increase weight [16]. Reductions in the "hunger hormone" ghrelin after oesophagectomy are also not explanatory [25, 26]. We do not understand exactly why these patients experience unintentional weight loss [12], even when they no longer suffer from cancer cachexia and are cured of cancer.

Broadly speaking, studies have shown that there are 3 known mechanisms of weight loss post-oesphagectomy [27]:

1) Stress response: Surgery can cause a significant stress responses, which lead to greater catabolism and energy consumption and decreased digestive function [28-30].

2) Poor eating function: Postoperative eating difficulties such as dysphagia, trouble swallowing saliva, and choking when swallowing can worsen weight loss post- oesphagectomy [31-35]. Both of these factors tend to improve with time and cannot be blamed for the unintentional weight loss seen in the long term in cancer-free, post-esophagectomy patients.

3) Gut endocrine changes: The gastrointestinal tract, the largest endocrine organ in the body, is a complex neuroendocrine system. More than 30 known peptide hormone genes are expressed in the digestive tract, with more than 100 different hormonally active peptides produced [36]. Patients with oesophageal cancer experience a decrease in ghrelin secretion and a significant increase in postprandial plasma glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), contributing to severe appetite loss and decreased food intake after esophagectomy [26, 37, 38]. There are similar mechanisms behind the intentional weight loss seen in patients post bariatric surgery.

3. Nutritional Treatments to Prevent Weight Loss in Patients with Oesophageal Cancer Postoperatively

The leading post-operative problems in patients with oesophageal cancer are dysphagia, weight loss and in some cases malnutrition, therefore adequate postoperative feeding is especially important [39]. The exact type and timing of this feeding has been a source of much debate in recent years. In 2011, Casaer et al recommended that TPN should no longer be the preferred route of postoperative feeding for these patients, concluding that early initiation of parenteral nutrition does not improve recovery and is associated with a higher incidence of septic complications [40]. It is now widely accepted that the use of TPN after oesophageal surgery should be administered only if EN is contraindicated. This is based on studies by Gabor et al and Fujita et al that found a reduction in severe complications and length of hospitalization in patients treated with EN rather than TPN [41, 42]. Within the realm of EN nutrition, there are primarily two different feeding routes used – Jejunostomy and Nasojejunal feeding. An RCT from 2007 found that Jejunostomy feeding is safe but entry site leakage, infection and occlusion might occur, with a reoperation rate of less than 2% [43].

Nasojejunal feeding is less invasive but dislocation occurs frequently, implying frequent replacements are needed [39]. Currently, the choice of EN remains primarily as a result of surgeon preference with no clear data suggesting superiority of one over the other available at present.

4. Energy Expenditure and Protein Metabolism

Oesophageal Cancer: Weight loss in cancer patients is frequently ascribed to a combination of reduced food intake and hypermetabolism [44]. In 2011, it was found that patients with operable esophageal cancers were normometabolic as compared to healthy controls [44], however, the resting energy expenditure (REE) of these patients was significantly increased after an esophagectomy. The mREE/pREE ratio was increased to 1.17 on POD7, but decreased to the preoperative level on POD14 [44]. This finding was supported by Sato et al. which showed a 31% increase in the mREE in patients undergoing an esophagectomy [45, 46].

Bariatric Surgery: Many studies have reported evidence of a decline in REE in patients post bariatric surgery [47, 48]. Moehlecke et al. [49] reported a mean reduction in REE at 6 months postoperatively in adults of 405 kcal/d (17.6%). The underlying mechanisms contributing to this metabolic adaptation are not well understood. Decreased circulating leptin levels [50], decreased thyroid hormones linked with blunted sympathetic nervous system activity, and decreased catecholamines associated with weight loss have been potential mechanisms described [51, 52]. However, more studies examining the mediators of REE are needed.

5. Mechanisms Involved with Bariatric Surgery That are Shared with Oesophagectomy

Sleeve gastrectomy is now the most common bariatric surgical procedure for people with obesity. Sleeve gastrectomy originated from observed weight loss after upper gastrointestinal surgery for cancer (38) and share many of the anatomical characteristics of an oesophagectomy. Sleeve gastrectomy achieves weight loss by altering gut hormone levels that are responsible for hunger and satiety, leading to a new hormonal weight set point [53]. These alterations to gut hormone levels primarily consist of a decrease in ghrelin secretion and an increase in postprandial plasma GLP-1, OXM and PYY, thereby reducing the sensation of hunger and increasing satiety. A summary of the predominant hormonal changes are as follows:

5.1 Glucagon-Like Peptide-1 (GLP-1)

GLP-1 is secreted by the L-cells of the small bowel, with higher concentrations in the distal ileum and colon. It acts on the GLP-1 receptors located in the hypothalamus, striatum, brainstem and substantia nigra, among other areas of the brain [54]. GLP-1 is produced in response to a meal and then increases satiety, reduces hunger and decreases food intake, through its effects on the hypothalamus and brainstem [55]. GLP-1 also increases insulin secretion, inhibits glucagon release and slows gastric emptying [56]. The post prandial GLP-1 levels are much higher after both RYGB and VSG [57]. The altered anatomy and shorter gut seen in RYGB leads to the rapid delivery of nutrients to the distal ileum causing an increase of both GLP-1 (and PYY) levels [58].

5.2 Oxyntomodulin (OXM)

OXM is an anorexigenic peptide co-secreted with PYY and GLP-1 in intestinal L-cells [59]. The administration of OXM reduces hunger, food intake and ghrelin levels as well as decreases gastric acid secretion, GE and duodenal motility [60]. Postprandial OXM is increased 1–2 months after RYGB [61].

5.3 Peptide YY (PYY)

PYY is also released from the L-cells of the distal small bowel after eating and acts at the arcuate nucleus of the hypothalamus, to decrease food intake but also via vagal afferents terminating at the nucleus of the solitary track, to signal satiety [62]. PYY has also been reported to delay gastric emptying [63]. Studies show that patients with increased levels of PYY after Sleeve gastrectomy and RYGB had more weight loss [58, 64]. The postprandial release of the hormone peptide YY (PYY) is markedly higher after both RYGB and Sleeve gastrectomy, but not after adjustable gastric banding or caloric restriction [65-68].

5.4 Ghrelin

Ghrelin is a peptide produced by the X/A-like cells in the fundus of the stomach during fasting and acts on growth-hormone secretagogue receptors [69]. Ghrelin levels are decreased after eating, with carbohydrates having more of a suppressive effect than protein and lipids [70]. Ghrelin stimulates neuropeptide Y–AgRP neurons within the arcuate nucleus [71] but also through the vagus and brainstem to increase food intake [72]. After sleeve gastrectomy, the levels of ghrelin are reduced [73]. Conversely, ghrelin levels are increased in the setting of calorie restriction and post-adjustable gastric banding [74]. There is very limited data available at present, which hinders our ability to fully understand the mechanism involved in the release of ghrelin after bariatric surgery. Mclaughlin et al and Mohlig et al postulate that the degree of hyperinsulinaemia is a known major determinant of ghrelin suppression amongst people with obesity [75, 76]. Changes in ghrelin release following surgical weight loss might depend on the degree of preoperative insulin resistance and the degree to which insulin sensitivity is restored [77]. The degree of vagal dysfunction following the surgical procedures may also contribute to the changes in the observed ghrelin levels [77].

5.5 Leptin

Leptin is secreted by adipocytes and influences energy intake primarily by acting on the hypothalamus [78-80] to decrease food intake and increase energy expenditure [78]. Loss of fat mass and decreases in plasma leptin levels are seen in patients who restrict their calorie intake, either through dieting or post-bariatric surgery [68, 81]. As mentioned, in dieting patients, hyperphagia is generally observed, however this is not seen in post-bariatric surgery patients, suggesting that the additional physiological alterations after surgery are enough to counterbalance the reduced leptin levels [82].

Patients post oesophagostomy experience similar hormonal shifts and disruption of the gut-brain pathway which then contributes to severe appetite loss and decreased food intake after esophagectomy [26, 37, 38, 83]. This has prompted much interest in the role of these hormones in mediating food intake and weight loss post-esophagectomy.

6. The Gut-Brain Pathway

The rate of transit of consumed food into the small bowel is regulated by the pylorus. When the food comes into contact with the small bowel mucosa, satiety gut hormones are released from enteroendocrine L-cells [59]. These hormones include GLP-1, Peptide YY (PYY) and oxyntomodulin (OXM). L-cells are present from the duodenum to the rectum, however, they are most abundant in the ileum and colon [84]. Bile then enters the small bowel not only to aid digestion, but also to release satiety gut hormones [85]. Bile acids are subsequently reabsorbed and can become plasma signals. Visceral signalling is further enhanced by small bowel gut microbiota [86]. These visceral signals are received by the brain reward centres which, at a certain threshold, manifest as a desire to stop eating. After food consumption, these gut derived signals progressively wane in intensity, resulting in a renewed feeling of "wanting to eat" [87]. The usual outcome then being further intake of food [87]. Thus, the gut-brain pathway controls what, how much, and when an individual decides to eat.

7. The Gut-Brain Pathway after Bariatric Surgery

After bariatric surgery, food rapidly progresses into the small bowel [88] enhancing satiety gut hormone signalling [4, 82, 89-92]. Prompt contact of food with the small bowel, delayed mixing of biliopancreatic secretions with food, and gut microbiota changes coalesce to cause small bowel mucosal adaptations that underpin this response [93]. This enhanced visceral signalling downregulates brain reward centres [91], diminishes "wanting to eat" [92] and reduces food intake [94].

8. The Gut-Brain Pathway after Oesophagectomy

Approximately 33% of recurrence-free patients after oesophagectomy demonstrate postoperative unintentional weight loss of over 15%, associated with impaired long-term nutritional status and quality of life [18, 95, 96]. After oesophagectomy food progresses quickly into the small bowel [14], with exaggerated satiety gut hormones responses [83, 97] and resultant changes to bile acids and gut microbiota. The brain receives enhanced visceral signals after surgery which downregulates brain reward centres and reduces the feeling of "wanting to eat" [98], especially energy dense foods [83] (See Figure 2). Early satiation remains the most important predictor of long-term bodyweight loss after oesophagectomy [99] as it is difficult for patients to eat in the absence of hunger, but even harder for them to eat when they feel full. These visceral signals also result in postingestive awareness which alerts the subject that additional food intake will cause visceral malaise [100]. This, combined with satiation, may progressively condition a reduced desire to eat large meals [100]. Unintentional weight loss results from the sum of these gut-brain pathway changes. In the setting of oesophageal cancer surgery specifically, the significant burden of malnutrition and associated quality of life impact may be ameliorated by suppressing the exaggerated gut hormone signalling to improve eating behaviour [101].

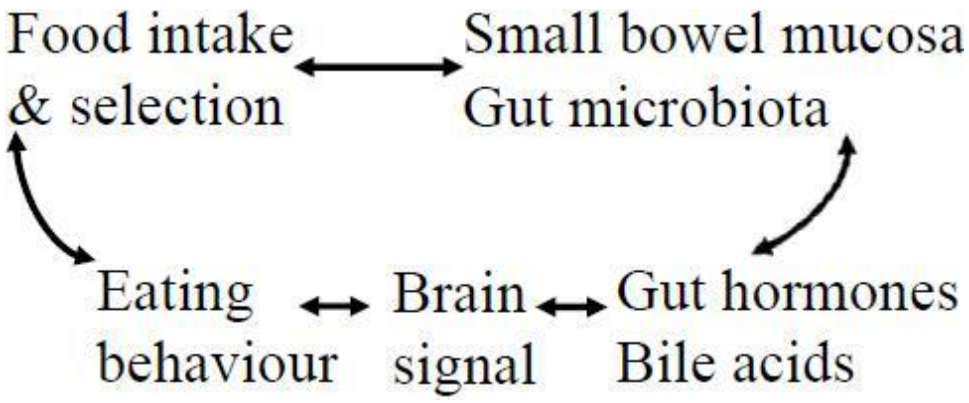

Figure 2 Mechanisms: Food rapidly progresses into the small bowel resulting in small bowel mucosal adaption (altered microbiota, L-cell hyperplasia, and increased gut hormone release). These converge to down-regulate brain reward responses and eating behaviour, ultimately resulting in reduced food intake.

Reduced energy intake and unintentional weight loss after oesophagectomy are due to a linked series of alterations along the gut-brain pathway, proceeding via: 1) gut mucosal adaptation; 2) increased visceral signals to the brain; 3) reduced brain reward responses to food; 4) reduced eating behaviour; 5) reduced food intake; and 6) changed food preferences.

9. Changes Because of The Similarities and Differences with Bariatric Surgery

Bariatric surgery originated from observed weight loss after upper gastrointestinal surgery for cancer [89]. Patients cured of oesophageal cancer however have *unintentional* weight loss compared to *intentional* weight loss after bariatric surgery. There are shared physiological and eating behaviour responses between bariatric surgery and oesophagectomy: exaggerated satiety gut hormone and plasma bile acid responses [89] which when acutely suppressed with somatostatin analogues increased eating behaviour and food intake [98]. Patients after sleeve gastrectomy typically exhibit greater weight loss when compared to those undergoing procedures such as gastric banding, with the latter not associated with significant alterations in satiety gut hormones, albeit that signalling after gastric banding may be associated with vagal changes [2]. This further emphasises the predominant role that gut hormone modulation plays in the weight loss seen post-bariatric surgery and also post-oesphagectomy.

10. Exploiting This New Understanding Therapeutically

With an increased understanding of the endocrine mechanisms driving weight loss post-oesphagectomy, a variety of exciting therapeutic options are emerging in recent studies:

10.1 Ghrelin Receptor Agonists

Appetite and food intake can be increased by using Ghrelin receptor agonists such as Capromorelin [102-107]. The administration of Anamorelin demonstrated clinical benefits in terms of appetite stimulation, improving lean body mass and weight gain in patients with cancer cachexia [102-107]. A study by Koizumi et al., explored the role of ghrelin in postoperative weight loss after oesophagectomy. Although there was an initial marked reduction in circulating ghrelin levels after

oesophagectomy, levels returned to preoperative concentrations approximately 3 months post-surgery, facilitating the return of hunger [108]. Patients after bariatric surgery or oesphagectomy often report that they are unable to finish a meal due to a premature feeling of 'fullness' or due to significant postprandial symptoms [108, 109]. This suggests that satiety hormones may play a more significant role in postoperative nutritional impairment in the long term [101].

10.2 Leptin Receptor Antagonists

Leptin is a hormone that is secreted by adipocytes that promotes satiety. Some animal studies indicate that the administration of leptin receptor antagonists leads to increases in food intake and body weight in rodents [110-112]. In a mouse study, Otvos et al showed that leptin receptor antagonists led to accelerated normal weight increase without producing any toxic effects [113]. Hence, these antagonists might be potential therapeutic options for unintentional weight loss. However, further studies including human studies are needed to further investigate this potential therapeutic targets validity, especially because endogenous leptin is significantly reduced after oesphagectomy. Hence reducing the already diminished leptin signal after oesophagectomy may have limited effects.

10.3 Somatostatin Analogues

Somatostatin is a regulatory peptide produced by enteroendocrine D cells in the GI tract that acts to suppress gut hormones in a negative feedback loop, maintaining homeostasis in appetitive signalling [114]. Somatostatin delays gastric emptying and intestinal transit, and directly suppresses the release of satiety gut hormones and insulin, while reducing postprandial splanchnic vasodilation by inhibiting the release of vasoactive factors [115]. These agents could potentially ameliorate some of the unintentional weight loss side effects seen in patients post-oesophagectomy. Elliott et al. showed that administration of octreotide, a synthetic somatostatin analogue, in patients after oesophagectomy led to attenuation of exaggerated postprandial satiety gut hormone responses. This almost doubled ad libitum food intake and was associated with increased appetitive behaviour toward a sweet-fat stimulus [116]. Geer et al demonstrated that long-acting octreotide is an effective treatment in the prevention of early dumping syndrome symptoms among post-gastrectomy patients [117]. This hypothesis was supported by another placebo controlled trial by Gray et al. [118] who also showed that octreotide had been effective in the prevention of postprandial hypoglycemia following a high carbohydrate meal challenge when compared to placebo after upper GI surgery [118]. Therefore, octreotide does show some therapeutic potential for these patients.

11. The Future

Prevailing doctrine suggests motivation is sufficient to increase food intake and reverse unintentional weight loss after surgical cure of oesophageal cancer [119]. Failure to gain weight is often met with disapproval [12]. However, much like the weight loss that patients experience post-bariatric surgery, it is becoming increasingly clear that the weight loss seen in patients post-oesphagectomy is not their conscious decision but rather the result of interdependent biological signals acting along the gut-brain pathway. By challenging dogmas and understanding these

endocrine mechanisms, described above, more thoroughly, we may begin to address the difficulties both patients who are underweight or overweight face in overcoming intrinsic, biological alteration in function, thereby reducing patient discrimination and fostering future innovation in clinical practice. Further studies are needed to further explore the impact of these gut hormones changes on the unintentional weight loss, seen in patients post-oesophagectomy as well as the potential exploitation of these hormonal changes as potential treatment targets in the future.

Author Contributions

David J. Tansey and Carel le Roux contributed equally to the reviewing of the literature, the concept of the review, writing the manuscript as well as reviewing and editing the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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