# Vitamin & Mineral Supplementation in Post Oesophagectomy Patients

## What is the evidence?

**Laura Nicholson**, Specialist Dietitian, Queen Elizabeth Hospital Birmingham

Oesophageal carcinoma has become more common in the past 40 years in the UK and it is currently the 14th most common cancer in adults.[1] Oesophageal carcinoma is characterised by an overall poor prognosis because of the high incidence of advanced disease (T3 or N1) at the time of diagnosis, resulting in approximately 15-20% of patients being offered a curative surgical resection (oesophagectomy).[2] However, due to an increase in the use of endoscopy as a screening test, Barrett's surveillance and advances in neoadjuvant chemotherapy, oesophageal cancer is being diagnosed earlier.[1, 3] This, in addition to surgical advances and the use of neoadjuvant chemotherapy, has resulted in oesophagectomy patients living longer.[4] As a result there is an increased interest in the longer-term consequences of oesophagectomy, with a greater focus on survivorship and quality of life.[5]

### Background

Oesophageal malignancies predispose patients to malnutrition because of the effects of chemotherapy, radiotherapy, surgery, dysphagia and malignancy-induced cachexia.[6] The rate of malnutrition in patients with oesophageal cancer on diagnosis has been estimated as high as 78.9%.[6] Ninety per cent of this group lose at least 5% of their body weight within 3 months following their surgery, and 16% have been found to lose over 15%.[6] The high incidence of malnutrition and nutritional related issues can largely impact on patients' quality of life and their treatment options.

As a result of an oesophagectomy, patients experience severe changes in their gastrointestinal (GI) anatomy, which can impair nutritional intake and nutritional status further. Without vital structures, patients may suffer from anorexia, early satiety, malabsorption, small bowel bacteria overgrowth, bile acid malabsorption (BAM), pancreatic insufficiency, vomiting, reflux, nausea and pain after eating. This greatly hinders nutritional intake, making it difficult to maintain a healthy nutritional status.[7] A study found that after 12 months post oesophagectomy, patients were still experiencing nutrition-related complaints.[8] In the past, as life expectancy post-surgery was minimal, little attention was given to micronutrient deficiencies,[9] with dietitians and surgeons mainly focusing on counselling to maintain body weight.[8] However, body weight itself does not provide any information about the adequate intake of micronutrients.

## Oesophagectomy and micronutrient deficiency

Minimal trials have yet to determine whether altered anatomy after radical upper GI surgery effects nutrient absorption. However, there are many factors which can result in an inadequate nutritional intake post oesophagectomy, including altered anatomy, early satiety, loss of appetite, taste and smell changes and post-surgery dumping syndrome.[6] It has been identified that during dietetic follow up post-surgery, the focus of care plans are predominantly on weight and body mass index (BMI),[10] with standard advice recommending a high calorie and protein rich diet in small frequent meals.[7] In addition to altered anatomy this advice could put patients at increased risk of micronutrient deficiency, as other food groups may be substituted to ensure that calorie and protein needs are met. In practice, micronutrient status is rarely investigated unless deficiency is suspected, resulting in patients becoming deficient and, therefore, symptomatic before an appropriate plan is implemented.

## Altered anatomy

Although there is no published evidence, the theory behind the risk of developing micronutrient deficiencies post oesophagectomy due to altered anatomy is sound. During an oesophagectomy, the stomach is pulled up into the chest and is made into a tube shape resulting in an intrathoracic stomach. It is unknown how this structure functions with regards to digestion. Intrinsic factor – a substance released by gastric parietal cells – is essential for the absorption of vitamin B12.[11, 12] It is unclear from the literature[12, 13, 14] whether a transthoracic stomach alters the production/release of intrinsic factor, therefore suggesting the gastric parietal cells remain present post oesophagectomy, resulting in intrinsic factor being produced as normal.

## Effect of altered pH

Many trials through pH monitoring have found that oesophagectomy patients retain or spontaneously recover acid production.[15] Therefore, it has been advised that protein pump inhibitors (PPI) are prescribed for all oesophagectomy patients to help reduce reflux-related symptoms.[15] Vitamin B12 absorption has been found to be impaired in individuals taking PPIs due to the reduction in gastric acid, resulting in less vitamin B12 being released from foods.[16, 17, 18] Although, there have been studies conducted that have disputed these findings.[19, 20] Therefore, as current evidence is inconclusive, regular screening may be more appropriate.

Gastric acid plays a vital role in calcium absorption, changing its bioavailability ready for absorption. Research has found that PPIs reduce the presence of gastric acid and therefore can result in a negative calcium balance, potentially causing bone loss.[21, 22, 23] However, these conclusions have been contradicted by other studies who have concluded that there is no association between PPI use and calcium levels.[24, 25] Overall, the majority of the evidence supports the correlation between PPI use and bone fractures, but what PPI dosage and duration increases the risk remains unclear. There are however many other variables which also influence bone health, such as vitamin D status and other medications. Therefore, the evidence is not strong enough to advise supplementation of calcium for all PPI users.

## Diarrhoea and steatorrhoea

The incidence of diarrhoea and steatorrhoea post oesophagectomy have been researched for many years. The initial correlation was highlighted by Lawrence in 1977.[26] Heneghan *et al.* (2015) found that 74% of post oesophagectomy patients were experiencing malabsorption from 6 months post-surgery, with vitamin A, iron and fat-soluble vitamin deficiencies being identified 18-24 months post-surgery.[27] Factors impacting on malabsorption include exocrine pancreatic insufficiency, BAM and small intestinal bacterial growth (SIBO).[27]

Oesophagectomy patients are at risk of steatorrhoea due to large food molecules and altered pH in the duodenum, resulting in a larger surface area for enzyme digestion.[28] There is also rapid upper intestinal transit which decreases the time allocated for digestion in the small intestine.[28] A recent prospective study[27] identified that 44% patients 18-24 months post gastrectomy/oesophegctomy had a positive faecal elastase test.

Gastric acid destroys many bacteria before they leave the stomach. Once in the small intestine, biliary and pancreatic secretions limit bacterial growth.[29] As outlined previously, post oesophagectomy patients are on long-term PPIs which increases the gastric pH in the transthoracic stomach, resulting in an increase of bacteria being transported into the small intestine contributing to SIBO.[27] Symptoms of SIBO are similar to those experienced by individuals who have pancreatic insufficiency and BAM, e.g. decreased oral intake, malabsorption and weight loss.[29]

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A guide published on managing persistent upper gastrointestinal symptoms during and after treatment for cancer, highlight that SIBO is a common cause for many GI symptoms after chemotherapy and upper GI surgery.[30] However, the guidelines also state there is no gold standard for diagnosing SIBO.[30] Therefore, it is difficult to link which micronutrient deficiencies result from the condition.

Bile is secreted by the liver in direct response to ingested dietary fat. A defect in the circulation of bile acids results in BAM.[27] In their guide, Andreyev *et al.* have identified that upper GI surgery and chemotherapy are common causes of BAM.[30] However, guidance on specific micronutrients monitoring is not specified.

It is unknown which micronutrient deficiencies result specifically from BAM, SIBO and pancreatic insufficiency. The literature suggests that SIBO, pancreatic insufficiency and BAM can result in similar micronutrient deficiencies. It is important, however, to recognise that patients are at high risk of micronutrient deficiencies as a result of malabsorption. This has been identified by the 'Guide to managing persistent upper gastrointestinal symptoms during and after treatment for cancer'.[30] The guide advises that routine blood tests should be completed as first line when a patient is symptomatic of malabsorption, including full blood count, urea, electrolytes, liver function, glucose, calcium, ferritin, transferrin, folate, vitamin B12, magnesium, CRP, vitamin D, selenium, copper, zinc, and INR (for vitamin K).[30]

## Cancer, chemotherapy and surgical stress

Neoadjuvant chemotherapy prior to oesophagectomy increases the rate of R0 resection and has become the 'standard care pathway' for locally advanced oesophageal cancer.[31] Therefore, all patients are encouraged to have chemotherapy prior to surgery and some cases will be offered further chemotherapy post-surgery. This impacts the patient's nutritional status further. Magnesium, potassium, vitamin D and folic acid deficiencies have been linked to specific cytostatic agents.[32] However, the evidence is not significant enough to recommend prophylactic supplementation during treatment. In addition, chemotherapy is known to cause malabsorption and diarrhoea.[33]

Surgery can result in malnutrition due to hypercatabolism, and may be associated with complications such as pain, anorexia and disorders in the digestion process.[12] Zinc and vitamins A and C have been found to be vital in the process of wound healing.[34] Therefore, in the post-operative phase it is suggested that the stores of these three micronutrients are depleted to help promote recovery. Molnar *et al* (2014) supported this by concluding that deficiencies in these micronutrients are not uncommon after an individual has had a chronic wound.[34] Therefore, it is possible an oesophagectomy patient enters the post-operative recovery phase with micronutrient deficiencies already present.

Patients with oesophageal cancer are likely to have lost a significant amount of weight at the time of diagnosis.[33] Surgery and chemotherapy imposes further metabolic demands on the cancer patient and can exacerbate current nutritional deficiencies.[33] According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on enteral nutrition, it can be assumed that all patients with cancer who consume less than 60% of their daily energy requirements for more than 7-10 days have an inadequate supply of micronutrients.[35]

In addition to the above, in 2012, there was a national patient safety alert on 'Risk of harm following gastric bypass' in which a patient died as a result of micronutrient deficiency 4 years post-surgery.[36] This patient had undergone a resection for bariatric purposes, therefore it cannot be compared directly with the oncology patient group as surgery and treatment aims differ. However, it highlights the dangers of micronutrient deficiency and the importance of prevention and management. Leading on from this alert it is now identified that all bariatric procedures have the potential to cause micronutrient deficiencies and long-term monitoring is now an essential component of bariatric practice.[36]

## Conclusion

**Oesophagectomy has a profound impact on the nutrient intake and absorption of micronutrients. As outlined above, there are many contributing factors which can result in micronutrient deficiencies. However, due to the poor quality of research there are no standardised pathways for the monitoring and supplementation of micronutrients post oesophagectomy. There is the obvious need for a large, multicentre, randomised control trial to determine what micronutrients oesophagectomy patients are at risk of becoming deficient from, and how this is managed, as it is unknown how an oesophagectomy patient will absorb supplementation.**