Vitamin insufficiency after surgery for oesophagogastric neoplasms: a prospective intervention study VITAMin Insufficiency in oesophagogastric Neoplasms or the VITAMIN study

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Study protocol

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Abstract

Background: Oesophageal cancer (EC) and gastric cancer (GC) are among the top ten cancers worldwide. Both diseases have impact on the nutritional status of patients and their quality of life (QoL). Preoperative malnutrition is reported in 42-80%. However, studies investigating postoperative nutritional status are limited and postoperative identification and treatment of micro- and macro-nutritional deficiencies are currently lacking in (inter-)national guidelines. The aim of this study is to identify and target micronutrient deficiencies after surgery for oesophageal or gastric neoplasms.

Methods: This is a single-centre prospective intervention trial performed in Zuyderland Medical Centre. A total of 248 patients who underwent oesophagectomy (n=124) or (sub)total gastrectomy (n=124) from 2011 until 2022 will be included (Cohens'd 0.4, power 80%, two-sided α 0.05, 20% dropout). Both groups will receive Calcium Soft Chew D3 and a tailormade multivitamin supplement (MVS); the oesophagectomy group will receive Multi-E and the gastrectomy group will receive Multi-G. The MVSs will be taken once daily and Calcium Soft Chew D3 twice daily. Supplementation will start after baseline measurements. At baseline (T=0), blood withdrawal for micronutrient analysis and faecal elastase-1 analysis for exocrine pancreas insufficiency (EPI) will be performed. Additionally, patients will receive questionnaires regarding QoL and dietary behaviour. After 180 days of supplementation (T=1), baseline measurements will be repeated, and the supplement tolerance questionnaire will be completed. Measurements will also be conducted after 360 days (T=2) and after 720 days (T=3) of supplementation. The main study parameter is micronutrient deficiency (yes/no) for all measurements. Secondary parameters include occurrence of EPI (n, %), occurrence of diarrhoea (n, %), steatorrhea (n, %) or bloating (n, %), time between surgery and start of supplementation (mean in months), QoL (questionnaires) at all time points. We hypothesize that vitamin B12, folic acid, vitamin D and ferritin are the most common deficiencies, and supplementation may resolve measured deficiencies.

Discussion: If micronutrient deficiencies are present in this population and daily supplementation resolves these deficiencies, routine monitoring and supplementation of micronutrient deficiencies can be implemented in the standard postoperative care of oesophageal and gastric surgery.

Trial registration: registered as NL9787 in the Netherlands Trial Registration, registered on October 18th, 2021 on https://www.trialregister.nl/trial/9787

Background

Oesophageal cancer (EC) and gastric cancer (GC) are among the top ten cancers worldwide, with rapidly increasing incidence (1, 2). Because of the involvement of the proximal digestive tract, both diseases may lead to decreased nutritional status of patients and their quality of life (QoL). Surgery is the cornerstone in the multimodal treatment of patients with EC or GC who are treated with curative intent. However, anatomical changes after oesophageal or gastric surgery may affect nutritional intake and absorption in the gastrointestinal tract in several ways.

Due to the surgical resection of the oesophagus and/or stomach and the reconstruction of the tract, especially the Roux-En-Y reconstruction in gastrectomies, the intake and uptake of nutrients is often decreased. Also changes in hormonal pathways lead to changes. Additionally, due to vagal denervation after surgery, inadequate stimulation of the digestive enzymes of the pancreas occurs leading to exocrine pancreatic insufficiency (EPI) (3). As a consequence, malnutrition may develop. Malnutrition is reported in 42–80% of patients with GC or EC prior to surgery and is associated with a high incidence of morbidity, decreased survival and poorer treatment outcomes (4–11). Consequently, nutritional status of these patients has been receiving more attention in clinical research (11–13).

A few studies reported micro- and macro-nutritional deficiencies after both oesophagectomy for EC and gastrectomy for GC (13–15). Deficiencies were found in 60–78% of the study population. The most profound deficiencies reported were vitamin D (37%-51%), ferritin (42–43%), folic acid (10–29%) and vitamin B12 (6–18%). Moreover, two studies showed that 16–27% of patients who underwent oesophageal or gastric surgery developed EPI (3, 12). These studies show that most patients who underwent oesophagectomy or gastrectomy develop micronutrient deficiencies. However, because of the surgical resection of a part of the digestive tract, it is not possible to correct these deficiencies with normal dietary intake.

The above-described deficiencies can cause clinical diseases that have been known for centuries as iron-deficiency anaemia (ferritin), vitamin B12 & folic acid anaemia, rickets with skeletal deformities, fractures, muscle weakness, fatigue and depression (vitamin D and calcium), disturbed vision and mental declination (vitamin B12).

The current Dutch guidelines for EC and GC advise to check serum blood values solely for vitamin B12 and iron after gastrectomy (16). For patients after oesophagectomy, it is advised to only check for vitamin B12 when possible symptoms of deficiency are present (17). The prevalence of vitamin deficiencies is expected to be higher, since symptoms only develop in severe deficiencies. Currently, identified deficiencies and possible symptoms are treated in different modalities such as injection, infusion or daily/weekly/monthly oral suppletion. This may be an intensive treatment regimen, since injection often needs to be performed in outpatient clinics and infusion requires hospital admission.

In bariatric surgery, in which reconstruction of the gastrointestinal tract is performed to induce weight loss and metabolic effects, deficiencies are also prevalent in high percentages. In contrast to the EC and GC population, deficiencies are regularly monitored after bariatric surgery and specific postoperative supplements have been developed. In addition, national and international guidelines for bariatric surgery advise to actively monitor serum values and provide standard supplements in postoperative patients who underwent bariatric surgery to prevent deficiencies (14, 18, 19). The anatomy of the reconstruction in bariatric surgery is comparable to the resections performed for EC and GC. Accordingly, active monitoring for deficiencies and standard supplementation to prevent deficiencies subsequent to oesophagectomy or gastrectomy should possibly be performed. Moreover, no evident national nor international guidelines are present that aim to improve nutritional status and QoL after oesophageal or gastric surgery (14). Therefore, the primary aim of this study is to identify micronutrient deficiencies by implementation of guided monitoring, and to prevent and to correct nutritional deficiencies by administering two supplements: one for GC and one for EC.

Methods

Study design

The VITAMIN (VITAMin Insufficiency in oesophagogastric Neoplasms) study is a single-centre prospective cohort study with no randomisation, whereby all patients will receive supplementation. The study is performed in the Zuyderland Medical Centre (MC) in Heerlen and Sittard-Geleen, a regional centre for oesophagectomies and gastrectomies. The total duration of the study will be three years. Patients will be divided into the oesophagectomy group or in the (sub)total gastrectomy group.

Two multivitamin supplements (MVSs) have been developed, one for patients who underwent oesophagectomy (Multi-E) and one for patients who underwent gastric surgery (Multi-G). Moreover, patients will receive Calcium Soft Chew D3 as an additional supplement.

Study population

Patients older than 18 years of age that underwent oesophagectomy or gastrectomy for malignancy with no signs of recurrence of disease between 2011 and 2022 in the Zuyderland MC are eligible to participate. Exclusion criteria are wedge resection of the stomach, recurrent malignant disease, metastases and treatment with chemotherapy during inclusion and study period. Moreover, patients who are not capable of taking oral supplements will be excluded.

Study algorithm (Fig. 1, table 1)

Included patients will undergo blood withdrawal, collect faeces for faecal elastase-1 test and fill in several questionnaires at baseline (T = 0), after six months (T = 1), after twelve months (T = 2) and after 24 months (T = 3) of the start of supplement intake. Moreover, patients will receive supplements based on the type of surgery they underwent. Patients will take the MVS and Calcium Soft Chew D3 daily. Patients who take vitamin supplements in any form at baseline, will be asked to stop supplementation.

Table 1

Product composition of the Multi-E and Multi-G multivitamin supplements.

Product composition (Multi-G)			Product composition (Multi-E)		
Active ingredient-Vitamins	**Dosage**	**RDI**	**Active ingredient-Vitamins**	**Dosage**	**RDI**
Vitamin A	1200 µg	150%	*Vitamin A*	1200 µg	150%
Vitamin B1	4,4 mg	400%	*Vitamin B1*	3,3 mg	300%
Vitamin B2	2,8 mg	200%	*Vitamin B2*	2,8 mg	200%
Niacin (vitamin B3)	32 mg	200%	*Niacin (vitamin B3)*	24 mg	150%
Vitamin B5	18 mg	300%	*Vitamin B5*	9 mg	150%
Vitamin B6	1,4 mg	100%	*Vitamin B6*	1,4 mg	100%
Biotin (vitamin B8)	100 µg	200%	*Biotin (vitamin B8)*	100 µg	200%
Folic acid (vitamin B11/B9)	700 µg	350%	*Folic acid (vitamin B11/B9)*	600 µg	300%
Vitamin B12	1000 µg	40000%	*Vitamin B12*	200 µg	8000%
Vitamin C	80mg	100%	*Vitamin C*	80 mg	100%
Vitamin D3	75 µg (3000IU)	1500%	*Vitamin D3*	75 µg (3000IU)	1500%
Vitamin E	30 mg	250%	*Vitamin E*	24 mg	200%
Vitamin K1	150 µg	200%	*Vitamin K1*	75 µg	100%
Active ingredient- Minerals			**Active ingredient - Minerals**		
Chromium	160 µg	400%	*Chromium*	40 µg	100%
Iron	75 mg	535%	*Iron*	32 mg	229%
Iodine	150 µg	100%	*Iodine*	150 µg	100%
Copper	3 mg	300%	*Copper*	2 mg	200%
Manganese	2 mg	100%	*Manganese*	2 mg	100%
Molybdenum	100 µg	200%	*Molybdenum*	50 µg	100%
Selenium	82,5 µg	150%	*Selenium*	55 µg	100%
Zinc	25 mg	250%	*Zinc*	16 mg	160%

Legend table 1: Multi- E will be given to patients who underwent oesophagectomy and Multi-G to patients who underwent (sub)total gastrectomy. Vitamin and mineral compositions and dosage are shown of both multivitamin supplements. Both groups will receive the multivitamin supplement daily. RDI= reference intake.

Multivitamin supplement

The oesophagectomy group will receive Multi-E and the gastrectomy group will receive Multi-G. Additionally, both groups will receive the same Calcium Soft Chew D3 prescription. All three supplements are developed by GIKAVI BV (Rotterdam, the Netherlands) based on current literature regarding nutrient deficiencies in patients who underwent surgery for EC and GC, and on the MVSs provided after bariatric surgery. The MVS will be administered once per day and Calcium Soft Chew D3 will be administered twice per day. However, due to possible interaction of calcium and iron, the Calcium Soft Chew D3 will be administered at a minimal difference of two hours from the MVS. At baseline, patients will receive supplements for 180 days. After 6 months, patients will receive supplements for another 180 days. After 360 days of supplementation, patients will receive supplements for 360 days. The supplements will be provided on the day of the hospital visit for blood analysis and collection of faeces in the hospital. Compliance will be studied by tablet count. Patients will be asked to return the packages at time point T = 1, T = 2 and T = 3.

Blood analysis

Venous blood sampling will be taken to analyse different nutrient states at all time points in the Zuyderland MC. The first venous blood sampling will be conducted before supplementation. Nutrients such as vitamins (A, B1, B6, B12, D, E, folic acid and international normalized ratio (INR)), minerals (serum iron, transferrin, ferritin, transferrin saturation, zinc, magnesium, phosphate), proteins (albumin, total protein, c-reactive protein (CRP)) and parathyroid hormone (PTH) will be analysed. Deficiencies will be classified according to current guidelines of the laboratory of the Zuyderland MC.

Faecal elastase-1 test

Faecal elastase-1 tests will be performed to diagnose EPI. Moreover, symptoms of EPI such as, bloating, steatorrhea and diarrhoea will be reported consistently. Patients will receive a special container for faecal collection by mail. The collected faeces will be returned to the hospital for

a faecal elastase-1 test. An EPI is defined as a quantity of faecal elastase-1 < 100 µg E1/g in combination with accompanying symptoms as described above.

Questionnaires

Patients will be asked to complete various questionnaires at every time point. These will be sent by e-mail or regular mail. The questionnaires used in this study regard QoL, eating behaviour and supplement tolerance. The questionnaires EQ-5D, QLQ-C30, QLCOG25 and the cancer worry scale (CWS) regard QoL (20–23). The adjusted three-factor eating questionnaire (TFEQ) regards dietary eating behaviour (24). Both the QoL questionnaires and the TFEQ questionnaires will be sent to all patients at all time points. The GIKAVI supplement tolerance questionnaire regarding the MVSs and Calcium Soft Chew D3 supplement, will be sent at T = 1, T = 2 and T = 3. A reminder will be sent to patients if the questionnaires are not completed within two weeks.

Study parameters/ endpoint

The main outcome in this study is any deficiency (yes or no) of vitamins, minerals and proteins measured in the nutrient blood levels below the specified threshold used in the Zuyderland MC. Secondary parameters include:

- Incidence of micronutrient deficiency post oesophagectomy or (sub)total gastrectomy at baseline
- Time between surgery and start of supplementation (mean in months)
- Occurrence of decreased faecal elastase-1 at any time point
- Occurrence of the following symptoms: diarrhoea (n, %), steatorrhea (n, %), bloating (n, %), which are all associated with EPI, at any time point
- QoL and vitality measured with questionnaires at all timepoints

Safety and stopping rules

The ingredients used for the MVSs and Calcium Soft Chew D3 are already safely implemented in clinical practice. Therefore, (severe) adverse events are not expected in the study population. Premature termination will occur when loss to follow up and withdrawal of individual subjects lead to insufficient data to investigate the research questions.

Statistical analysis

Sample size calculation

A sample size was calculated even though no studies have been performed with the same primary objective. Based on a Cohens'd of 0.4, a two-sided alpha of 0.05 and a power of 80% the calculated sample size is 99 per group. Considering the maximum acceptable drop-out rate of 20% in clinical studies, the number of patients needed to be included is 124 per group (oesophagectomy and gastrectomy), with a total of 248. To include this number of patients, all eligible patients from 2011 until 2022 that underwent oesophagectomy or gastrectomy in the Zuyderland MC will be invited for participation. Patients who are currently postoperatively monitored will be notified about this study during hospital visits by their supervising physician. If postoperative follow up has been ended, patients will be invited by their previous supervising physician via telephone. Since micronutrient deficiencies are not regularly monitored and treated in this population, a low drop-out rate is expected. The motivation of this population to participate is considered high and based on the response of patients during hospital visits and on the high compliance of bariatric patients who participated in a similar study design.

Data analysis

All data will be collected and analysed using Statistical Package for Social Sciences (SPSS) version 26. The primary study parameter is the presence of any deficiency (yes or no) defined as a measured value below the reference value. Multivariable linear regression analyses will be used to assess group and over time differences of individual blood value measurements. Multivariable analyses will be performed to correct for confounders.

Secondary parameters such as incidence of micronutrient deficiency (n, %), occurrence of EPI (n, %), occurrence of diarrhoea (n, %), steatorrhea (n, %), bloating (n, %), and time between surgery and start of supplementation (mean in months, standard deviation or media, interquartile range) will be compared between treatment groups using multivariable logistic regression analysis.

QoL and vitality of patients will be assessed using the EQ-5D, QLQ-C30, QLC-OG25 and CWS questionnaires according to the scoring manuals from the authors (20–23). These questionnaires will be assessed using a Mann-Whitney U test between the oesophagectomy and gastrectomy group. Over time differences between groups will be assessed separately using Friedman ANOVA and individual Wilcoxon Signed Rank tests with a Bonferroni correction as post-hoc analyses.

Ethical and regulatory considerations

The study has been approved by the medical ethics committee of the Zuyderland MC (METCZ20210146) and has been registered in the Netherlands Trial Registry (NTR) (NL9787). The study will be conducted according to the principles of the Declaration of Helsinki (10th version, Fortaleza, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other applicable guidelines, regulations and Acts. The principal and coordinating investigator will be responsible for recruitment, data collection, follow-up of included patients, completion of case report forms and adherence to the study protocol. Eligible patients will be informed about the study by their supervising physician. Informed consent will be obtained by the coordinating investigator. The project leader will be responsible for the design and conduct of the study, for the preparation of the protocol and revisions, and preparation of

case report forms. Revisions of the study protocol will be communicated to all investigators. The data master file and data verification will be monitored by the Clinical Trial Centre Maastricht (CTCM). Data will be collected using individual trial case numbers processed by the electronic database program Research Manager. Patient data will be anonymized using unique participant numbers prior to data entry in Research Manager. The final dataset will be analysed by the coordinating investigator. The definition of authorship will be followed by the International Committee of Medical Journal Editors Guidelines (25). The results will be communicated via international conferences, via publications and via the NTR.

Discussion

Malnutrition is common after surgery for oesophageal and gastric neoplasms (12). Literature regarding the incidence of micronutrient deficiencies and micronutrient supplementation after oesophageal and gastric surgery for EC or GC is sparse. Optimal monitoring and interventions to treat micronutrient deficiencies are lacking for patients who undergo oesophagectomy or gastrectomy. Further research is required to determine optimal additional oral micronutrient supplementation for this population.

The European Society for Clinical Nutrition and Metabolism (ESPEN) developed guidelines for nutrition in cancer patients (26). The current ESPEN guidelines recommend to consider routine postoperative nutritional support via oral or enteral route for patients undergoing upper-gastrointestinal surgery. Oral suppletion is advised in the preoperative setting for both patients with EC and GC while postoperative advice regarding monitoring of micronutrients and additional micronutrient supplementation for these patients is lacking (27). However, literature investigating malnutrition after oesophageal or gastric surgery, shows that malnutrition and suboptimal micronutrient intake is highly prevalent (13–15). Moreover, current evidence shows that a thorough understanding of the postoperative micronutritional needs and treatment of micronutrient deficiencies for these patients are necessary (12, 27, 28).

Because no MVSs have been developed for patients who underwent oesophageal or gastric surgery, the composition of these supplements may be altered in the future similarly as the MVSs investigated in bariatric surgery (28).

The VITAMIN study will identify the most common micronutritional deficiencies in patients that underwent curative surgery for EC and GC. Moreover, the study will also inform about QoL during administration of the MVSs and Calcium Soft Chew D3 supplement. These results will further increase knowledge about deficiencies subsequent to oesophageal and gastric surgery and may lead to guidelines for routine monitoring of the nutritional status in clinical practice.

Abbreviations

CRP: C-reactive protein; CTCM: Clinical Trial Centre Maastricht; CWS: Cancer Worry Scale; EC: Oesophageal cancer; EPI: Exocrine pancreatic insufficiency; ESPEN: European Society for Clinical Nutrition and Metabolism; GC: Gastric cancer, MC: Medical Centre; METCZ: Medical ethics committee of Zuyderland MC; MVS: Multivitamin supplement; NTR: Netherlands Trial Register; PTH: Parathyroid hormone; QoL: Quality of life; SPSS: Statistical Package for the Social Sciences; TFEQ: The Three Factor Eating Questionnaire; VITAMIN: VITAMin Insufficiency in oesophagogastric Neoplasms; WMO: Medical research involving human subjects act.

Declarations

Ethics approval and consent to participate

The study will be conducted according to the principles of the Declaration of Helsinki (10th version, Fortaleza, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other applicable guidelines, regulations and Acts. Written, voluntary, informed consent to participate in the study will be obtained from participants. Individual patient information will not be made available.

Consent to publish

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Clinical Trial Centre Maastricht but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Clinical Trial Centre Maastricht.

Competing interests

It was declared by the authors that they don't have competing interests. There was no significant financial support by a commercial organisation for this work that could have influenced the design or analysis of the study, nor the writing of this manuscript.

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Authors' contributions

AV and GV participated in the study design and drafted the manuscript. TV, JS, EB and EJB contributed to the acquisition. ML arranged all laboratory measurements and its logistics. MS and GV initiated the trial and supervised the drafting of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Figures

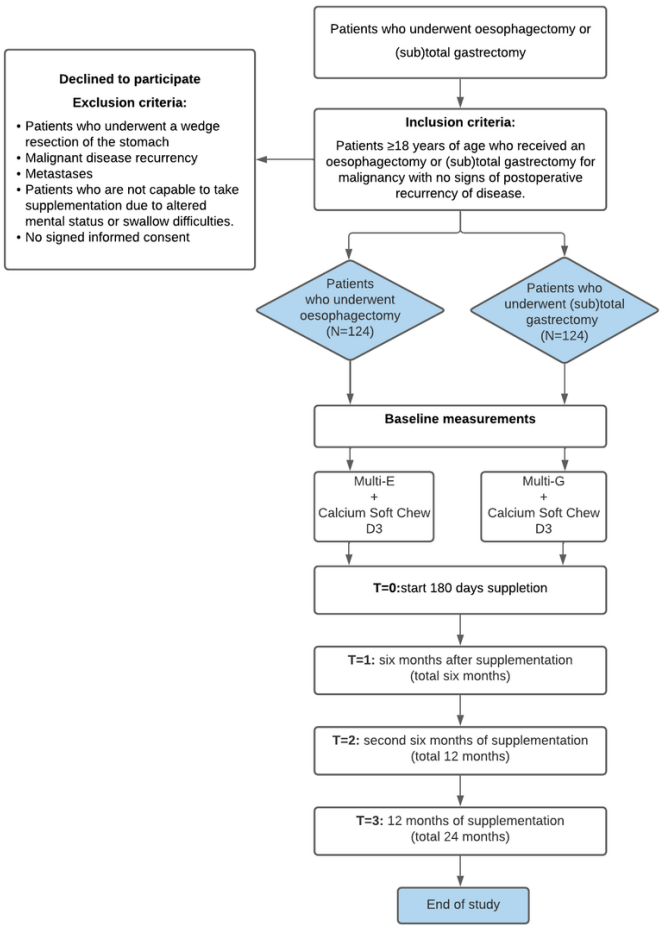

Figure 1

Flow chart of the study design. Patients will be divided into two groups: oesophagectomy or gastrectomy group. The oesophagectomy group will receive Multi-E and the gastrectomy group Multi-G. Both multivitamin supplements will be taken daily. Both groups will also receive Calcium Soft Chew D3 twice a day. Every time point consists of the following measurements: quality of life and food questionnaires, laboratory measurements of different vitamins, minerals and proteins and faecal-elastase-1 test. The GIKAVI supplement tolerance questionnaire will be added to the measurements at T=1, T=2 and T=3. The total study period will be two years.