REVIEW

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A systematic review on the role of vitamins, minerals, proteins, and other supplements for the treatment of cachexia in cancer: a European Palliative Care Research Centre cachexia project

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Abstract

We provide a systematic review to support the European Palliative Care Research Collaboration development of clinical guidelines for cancer patients suffering from cachexia. CENTRAL, MEDLINE, PsycINFO, ClinicalTrials.gov, and a selection of cancer journals have been searched up until 15 April 2016. The systematic literature research yielded 4214 publications with 21 of these included in the final evaluation. Regarding minerals, our search identified only one study examining the use of magnesium with no effect on weight loss. As far as vitamins are concerned, vitamin E in combination with omega-3 fatty acids displayed an effect on survival in a single study, vitamin D showed improvement of muscle weakness in prostate cancer patients, and vitamin C supplementation led to an improvement of various quality of life aspects in a sample with a variety of cancer diagnoses. For proteins, a combination therapy of β-hydroxy-β-methylbutyrate (HMB), arginine, and glutamine showed an increase in lean body mass after 4 weeks in a study of advanced solid tumour patients, whereas the same combination did not show a benefit on lean body mass in a large sample of advanced lung and other cancer patients after 8 weeks. L-carnitine led to an increase of body mass index and an increase in overall survival in advanced pancreatic cancer patients. Adverse effects of food supplementation were rare and showed mild intensity. There is not enough solid evidence for the use of minerals, vitamins, proteins, or other supplements in cancer. No serious adverse effects have been reported with dietary supplementation.

Keywords Cancer cachexia; Minerals; Vitamins; Micronutrients; Dietary supplements; Systematic review; Guidelines

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Introduction

Cachexia is often seen in cancer patients in advanced stages of the disease. The European Palliative Care Research Collaborative has defined cancer-related cachexia as follows: 'Cancer cachexia is a multi-factorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism'.[1] With regard to the underlying causes, there is an interplay between systemic inflammation and hypermetabolism due to neoplasma, nutritional and/or intake factors related to tumour or treatment induced anorexia, changes in

physiological uptake and/or storage and biopsychosocial aspects of functional impairment.[2]

The aetiology of micronutrient deficiency is multifaceted. Cancer may impede the usual intake of micronutrients. In addition, inflammatory activity and gastrointestinal symptoms of the cancer itself or the catabolic effect of the anti-neoplastic therapy may result in malnutrition, which also reduces micronutrient intake.[3] Lack of dietary supplements[4,5] may also play a role in cancer aetiology, and supplementation with these elements has been put forward as a preventive measure. Against this backdrop, there is an ongoing discussion on the need for dietary supplementation with micronutrients such as vitamins, minerals, proteins, or certain trace elements.[6] However, there is no clear indication for the importance of these substances for treatment of cachexia or cachexia-related symptoms. Therefore, expert guidelines from the American Cancer Society, the World Cancer Research Fund, and the American Institute for Cancer Research advise patients with cancer against the use of food supplements and advocate obtaining nutrients from normal food intake whenever possible.[7,8] Nevertheless, the American Cancer Society guide for informed choices describes a probable benefit when taking a standardized food supplement containing multiple vitamins and minerals during and after cancer treatment in order to cover the daily demand, even though the daily requirement of micronutrients for a cancer patient is not known. The Cancer Society argues that this demand could not be covered because of loss of appetite, maldigestion, or malabsorption as a consequence of tumour or treatment side effects.[9] To date this recommendation is based on weak evidence.

In our systematic review, the term 'food supplements' or the synonymously used term 'dietary supplements' is based on the definition of the European Food Safety Authority: 'Food supplements are concentrated sources of nutrients or other substances with a nutritional or physiological effect, whose purpose is to supplement the normal diet. Food supplements are marketed 'in dose' form, for example as pills, tablets, capsules, or liquids in measured doses etc. Supplements may be used to correct nutritional deficiencies or maintain an adequate intake of certain nutrients'.[10]

In a large survey on food supplements, 73% of cancer patients had used supplements in the past month reporting a significant decrease in appetite loss;[11] 67 subjects (29.8%) had breast cancer, 40 (17.8%) had colorectal cancer, 32 (14.2%) had lung cancer, and 86 (38.2%) had other forms of cancer.

As part of the development of guidelines for the treatment of cachexia in cancer patients, the European Palliative Care Research Collaborative performed a Delphi procedure on a set of guideline statements.[1] Two statements where no consensus was reached were used as starting points for a systematic review. Treatment of cachexia in advanced cancer patients using fish oil was subject of another systematic review prepared by Ries *et al.*[2] The guideline on dietary supplements stated that there is not enough evidence for a general recommendation. Patients who are not able to consume the recommended daily amount of minerals, vitamins, and proteins may try to compensate this deficit with supplements. However, the proposal failed to reach an adequate level of consensus, and a systematic review was commissioned accordingly.

We aimed to evaluate the efficacy of vitamin, mineral, proteins, and dietary supplements for cachexia in cancer patients.

Methods

This review is part of the development of clinical practice guidelines of the European Palliative Care Research Centre (PRC) on the treatment of cachexia in patients with cancer.

Criteria for considering studies in this review

The review included studies comparing treatment with or without vitamin, mineral, proteins, or other dietary supplements in cancer patients suffering from cachexia or cachexia-related symptoms. Studies comparing different supplements were also included. Publications were excluded if they reported on animals, children, or non-cancer patients.

Perioperative treatment of cachectic patients for curative or palliative surgery with minerals, vitamins, or other supplements was not the primary focus of the review. These studies were included, but evaluated separately.

Studies were included if they included cancer patients with cachexia, indicated by weight loss $>5\%$ in 6 months, ongoing hypermetabolism and/or reduced food intake.

A spreadsheet was designed with data from each included trial. Information on study design, study size by means of patient number, setting, study limitations, patient characteristics, outcome measures, and results were entered and evaluated. A meta-analysis was not possible as a variety of outcome measures were used, and study designs were not comparable.

A recommendation according to the GRADE methodology (positive or negative and strong or weak recommendation)[12,13] was drafted from the evidence of the reviewed literature.

Search methods for identification of studies

To identify studies, we developed a detailed search strategy (Appendix 1–3) for each electronic database and other resources. The search was restricted to publications in the

English language. As a brief quality check for our search strategy, we selected two well-known publications of high relevance for our review and checked whether these publications were covered by the search strategy.[14,15] Using this strategy, we could confirm the accuracy and validity of our literature search.

Electronic searches

We searched the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) up until 15 April, 2016; search strategy as detailed in Appendix 1;
- MEDLINE (OVID) from inception up until 15 April, 2016; search strategy as detailed in Appendix 2;
- PsycINFO (OVID) from inception up until 15 April, 2016; search strategy as detailed in Appendix 3.

Searching other resources:

We screened the references of identified articles for additional studies. Published abstracts were also obtained through searches of ClinicalTrials.gov database and conference proceedings.

Data collection

Selection of studies

We retrieved in full all studies with an abstract referring to the subject of vitamins, minerals, proteins, or other dietary supplementations aimed at treating cachexia in cancer patients. Eligible studies had to define cachexia as an outcome measure.

Data extraction and management

Two authors (MM and M) extracted data (Figure 1) using a standard data extraction form and reviewed the data from the studies. Findings were cross-checked in a second step by three autors (MM, RC, and CS). Four authors (LR, MMa, SK, and HC) cross-checked a sub-sample. We resolved disagreement by consensus.

Assessment of risk of bias in included studies

Two authors (MM and M) independently assessed risk of bias by the Cochrane risk of bias tool (Figures 2 and 3) for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*,[16] with any disagreements resolved by discussion or by involving

Figure 1 Study flow diagram.

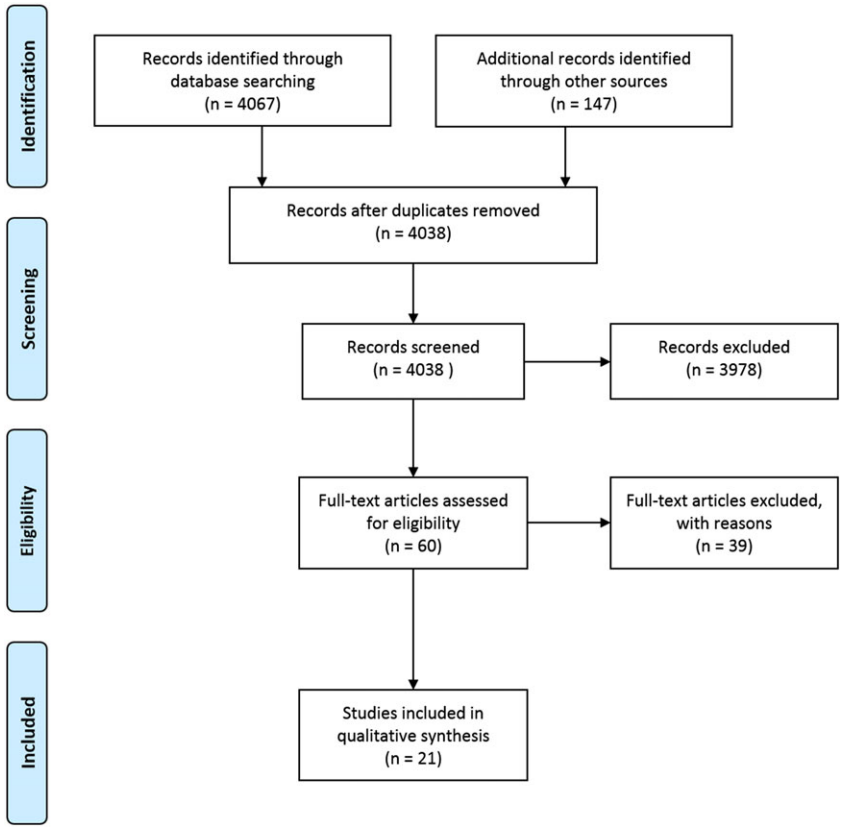
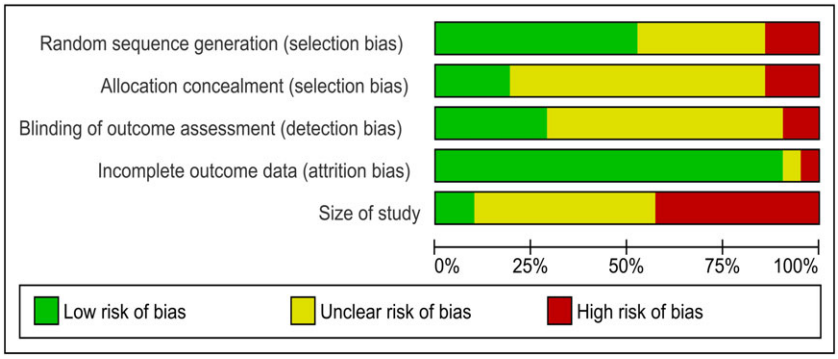


Figure 2 Risk of bias graph: review of authors' judgements about each risk of bias item presented as percentages across all included studies.



other review authors (LR, HC, and RC). We assessed the following for each study:

Random sequence generation (checking for possible selection bias).
We assessed the method used to generate the allocation sequence as follows: low risk of bias (any truly random process, e.g. random number table; computer random number generator); and unclear risk of bias (method used to generate sequence not clearly stated).

Allocation concealment (checking for possible selection bias).
The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as follows: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, and opaque envelopes); and unclear risk of bias (method not clearly stated).

Blinding of outcome assessment (checking for possible detection bias).
We assessed the methods used to blind study participants and outcome assessors from the knowledge of which intervention a participant received. We assessed the methods as follows: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. identical tablets, matched in appearance and smell); and unclear risk of bias (study states that it was blinded but does not provide an adequate description of how this was achieved).

Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcomedata).
We assessed the methods used to deal with incomplete data as follows: low risk (less than 10% of participants did not complete the study and/or used 'baseline observation carried forward' analysis); unclear risk of bias (used 'last observation carried forward' analysis); and high risk of bias (used 'computer' analysis).

Size of study (checking for possible biases confounded by small size).
We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50–199 participants per treatment arm); and high risk of bias (fewer than 50 participants per treatment arm).

Risk of bias in included studies
The findings are presented in the 'Risk of bias' graph (Figure 2), which reviews the authors' judgments about each risk of bias item shown as percentages across all included studies and the 'Risk of bias' summary (Figure 3), which reviews the authors' judgments about each risk of bias item for each included study.

Results

We screened 4214 publications. Twenty-one papers were considered for final evaluation (Figure 1).

Trials of mineral supplements

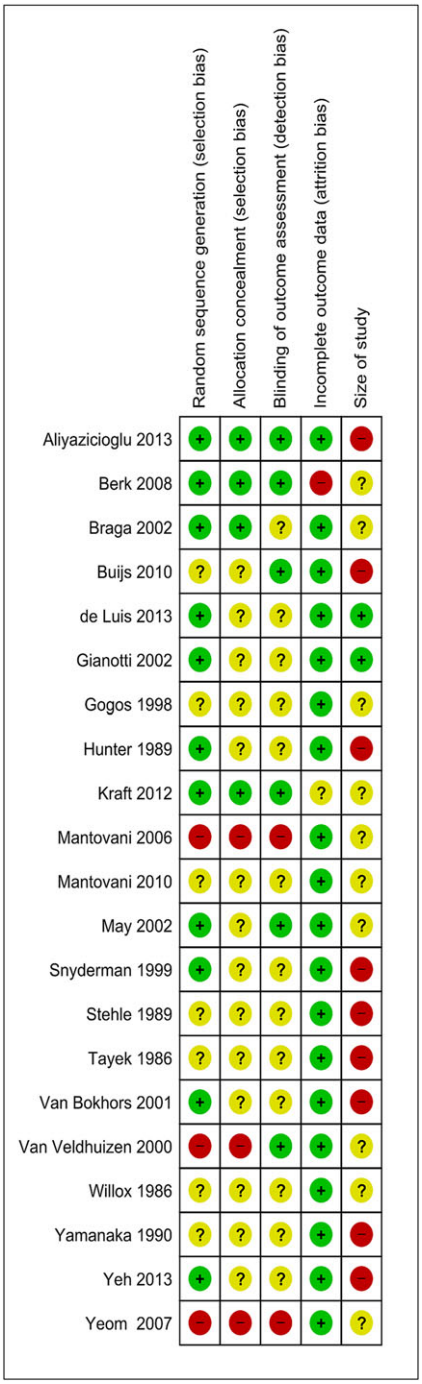
The literature search identified one randomized controlled trial on the use of magnesium in 17 patients with advanced testicular cancer and weight loss but found no significant differences in weight loss between groups[17] (Table 1).

Trials of vitamin supplements

Our literature search included one crossover study of 16 patients with advanced prostate cancer treated with vitamin D. Six patients reported improved muscle strength after vitamin supplementation.[18]

Vitamin C supplementation was tested in a sample of 39 patients with stomach (10), lung (7), liver (1), breast (4), cervix (1), colorectal (9), biliary (2), and other (5) cancer sites in

Figure 3 Risk of bias summary: review of authors' judgements about risk of bias items for each included study.



terminal stage. Vitamin C was substituted intravenously and orally, and patients improved on different subscales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) including physical and cognitive function, appetite loss, fatigue, and nausea/vomiting.[19]

Treatment of 60 patients with generalized solid tumours (breast, gastrointestinal, lung, liver, and pancreas) with a combination of omega-3 fatty acids and vitamin E did not have any effect on body weight compared with placebo.[20] The combination showed significant increase in survival for all patients compared with the placebo group. However, the authors did not differentiate between the specific impact of vitamin E supplementation compared with omega-3 fatty acids (Table 2).

Trials with proteins and other dietary supplements

In a randomized controlled study of 32 cachectic advanced solid tumours (stage IV) patients from several types of cancer such as colon, ovarian, lung, pancreatic, and other cancer, May *et al*. tested a combination of β-hydroxy-β-methylbutyrate (HMB), arginine, and glutamine and showed an overall benefit with an increase in lean body mass (LBM), improved mood, less weakness, and improved haematological parameters after 4 weeks compared with placebo[21] (Table 3). A mixture of HMB, glutamine, and arginine or an isonitrogenous, isocaloric control was supplemented in 472 advanced lung and other cancer patients. However, there was no statistically significant difference in the 8 week LBM between the two arms.[22]

Seventy-two participants with advanced pancreatic cancer taking L-carnitine showed an increase in body mass index (BMI) by 3.4 ± 1.4%; a decrease in BMI was observed in the control group. There was also a trend towards an increased overall survival in the L-carnitine group and reduced hospital-stay.[15] In another controlled trial, 332 patients were randomized into five treatment arms, comparing megesterol, eicosapentaenoic acid, carnitine, and thalidomide with a combination of all four substances in the fifth arm.[14] An analysis of pre-treatment to post-treatment changes showed that LBM significantly increased, while the resting energy expenditure decreased in the combination arm. Thus, study findings revealed that the combined supplementation was superior. Carnitine alone did not show any benefits.

In a small study of nine malnourished participants with intra-abdominal cancer, participants received both conventional total parenteral nutrition (TPN) containing 19% branched-chain amino acids (BCAA) and isocaloric, isonitrogenous TPN containing 50% BCAA (BCAA-TPN).[24] The trial showed that the fractional albumin synthesis rate increased significantly on daily BCAA-TPN. Another study from Tayek *et al*. investigated the effect of a BCAA-enriched solution in 10 malnourished patients with intra-abdominal metastatic adenocarcinoma.[25] The participants were given isonitrogenous amounts of both a conventional (TPN) formula containing 19% BCAA and a BCAA-enriched TPN formula containing 50% of the amino acids as BCAA in a

Table 1 Trials with minerals

Study	Design	Supplement	Type of application	Number of patients	Cancer type	Setting	Assessed tissue	Outcome measure	Narrative summary of results	Adverse side effects
Willox *et al.* 1986[17]	RCT	Magnesium	i.v; tablet p.o.	16	Testicular; ovarian cancer	Magnesium supplementation (study group) vs. no supplementation (control group) in the course of treatment with cis-diamminedichloroplatinum II (cis-platin) over 14 months	Urine, blood	EORTC	After 14 months serum magnesium concentration was significantly higher in the study group (0.62 ± 0.009 vs. 0.50 ± 0.07; $P < 0.01$). Weight loss did not differ significantly between the groups; control group showed significantly greater renal tubular damage.	Discontinuation due to 'metallic' taste of magnesium; number of dropouts due to adverse effects not reported.

EORTC, European Organization for Research and Treatment of Cancer; i.v., intravenous; p.o., per oral; RCT, Randomized controlled trial

random order. BCAA-enriched formulae group showed significant increases in whole body protein synthesis and leucine balance. Both studies demonstrated potential clinical benefits associated with BCAA-enriched TPN in cancer cachexia patients.

Supplementation with combinations of antioxidants, vitamins, omega-3 fatty acids, medroxyprogesterone acetate, and celecoxib[23] was used in a study of 39 cancer patients. The study reported positive effects stabilizing or increasing weight, LBM, and appetite.

In another study, an Ethanwell/Ethanzyme (EE) regimen was investigated in 68 malnourished patients with head and neck cancer.[26] Ethanwell is a protein-dense and energy-dense oral nutritional supplement that contains several ingredients including omega-3 fatty acids, glutamine, selenium, and CoQ10. Ethanzyme is an enzyme product composed of multiple probiotics and vitamins. The result showed that an EE regimen improved body weight as well as serum albumin and prealbumin levels in head and neck cancer patients with a BMI <19. However, methodology in both abovementioned studies did not allow to differentiate the beneficial effects of the individual substances in the combination therapies.

Perioperative supplementation

Nine studies on the use of different combinations of arginine, glutamine, alanine, glycine, BCAA, omega-3 fatty acids, and RNA in a perioperative setting were identified including a total of 791 cancer patients[27–35] (Table 4). Two of these studies investigated patients with major weight loss at the time of admission.[27,30] In five studies,[27,30,32,34,35] arginine was supplemented in different mixtures. Supplementation showed beneficial effects with regard to length of hospital stay,[27,34] postoperative infections,[27] increase in BMI,[35] and albumin, prealbumin, and lymphocyte levels.[35] One study[32] in 32 head and neck cancer patients also reported an overall long-term survival (34.8 months vs. 20.7 months). In two studies, glutamine supplementation was investigated.[29,33] Improved nitrogene balance and intracellular glutamine concentration[29] and shortened hospital stay[33] were relevant clinical effects.

Adverse effects with dietary supplements

Adverse effects were metallic taste after magnesium supplementation,[17] diarrhoea,[14,15] and nausea[15] after L-carnitine supplementation, or mild abdominal discomfort and transient diarrhoea after a mixture of omega-3 polyunsaturated fatty acids plus vitamin E.[20] HMB in combination with arginine was associated with nausea, constipation, and diarrhoea.[22] EE regimen[26] led to oral mucositis and emesis.

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Table 2 Trials with vitamins

Study	Design	Supplement	Type of application	Number of patients	Cancer type	Setting	Assessed tissue	Outcome measure	Narrative summary of results	Adverse effects
Yeom *et al*. 2007[19]	Prospective study	Vitamin C	i.v.; tablet p.o.	39	Various primary neoplasms	All patients received 10 g of vitamin C i.v. twice in 3 days and 4 g of vitamin C p.o. per day for a week.	Blood	EORTC	Pre-treatment versus post-treatment scores after 1 week supplementation showed improved global health (36 ± 18 vs. 55 ± 16; $P = 0.001$); patients reported significantly higher scores for physical (66 ± 20 vs. 72 ± 15, $P = 0.037$), role (59 ± 31 vs. 73 ± 22, $P = 0.002$), emotional (68 ± 24 vs. 78 ± 19, $P = 0.001$), and cognitive (69 ± 23 vs. 80 ± 16, $P = 0.002$) function and significantly lower scores for fatigue (52 ± 24 vs. 40 ± 19, $P = 0.001$), nausea/vomiting (24 ± 25 vs. 11 ± 15, $P = 0.001$), pain (30 ± 32 vs. 21 ± 25, $P = 0.013$), and appetite loss (50 ± 43 vs. 31 ± 29, $P = 0.005$).	None
Van Veldhuizen *et al*. 2000[18]	Phase-II-crossover-study	Vitamin D	Liquid p.o.	16	Prostate cancer	All patients received Vitamin D 2000 units daily for 12 weeks following a 4 week placebo period	Blood	Muscle strength at enrollment and every 4 weeks; serum calcium and vitamin D measured at each visit	12 weeks scores to 4 weeks scores (placebo period) showed no significant pre-post-treatment difference; reduced pain scores in four patients (25%) and improved muscle strength in six patients (37%).	None
Gogos *et al*. 1998[20]	RCT	Omega-3 fatty acids plus vitamin E	Capsule p.o.	60	Various primary neoplasms	18 g fish oil + 200 mg vitamin E (study group) vs. placebo (control group) daily until death	Blood	T-cell-subsets, cytokine production, nutritional response, Karnofsky index, survival	After 40 days, study group showed a significant increase in TNF-α levels (369 ± 32 vs.784 ± 207, $P < 0.05$), Karnofsky index (51 ± 3 vs. 72 ± 4, $P = 0.01$) and a significant prolonged survival (no exact numbers presented; $P = 0.025$), while there was no effect on IL-1, IL-6, and body weight.	Mild abdominal discomfort; transient diarrhoea; number of dropouts due to adverse effects not reported.

EORTC, European Organization for Research and Treatment of Cancer; IL, Interleukin; i.v., intravenous; p.o., per oral; RCT, Randomized controlled trial; TNF, Tumour Necrosis Factor

Table 3 Trials with other dietary supplements or combinations

Study	Design	Supplement	Type of application	Number of patients	Cancer type	Setting
May *et al*. 2002[21]	RCT	HMB, arginine, and glutamine	Liquid p.o.	32	Various primary neoplasms	Treatment with HMB (3 g/day), L-arginine 14 g/day), L-glutamine (14 g/day [HMB/Arg/Gln]) (study group) vs. isonitrogenous mixture of nonessential amino acids (control group) over a 24 weeks period
Berk *et al*. 2008[22]	RCT	HMB, arginine	Liquid p.o.	472	Various primary neoplasms	Mixture of HMB, glutamine, arginine (study group) vs. an isonitrogenous, isocaloric mixture (control group) twice a day for 8 weeks
Mantovani *et al*. 2010[14]	RCT	Megesterol, eicosapentaenoic acid, carnitine and thalidomide, plus polyphenol, lipoic acid, carbocysteine, vitamin E, vitamin A, and vitamin C orally	Tablet; liquid p.o.	332	Various primary neoplasms	5 groups: (1) Megesterol, (2) eicosapentaenoic acid, (3) carnitine, (4) thalidomide, and (5) mixture of (1)–(4); additionally in all groups polyphenol, lipoic acid, carbocysteine, vitamin E, vitamin A, and vitamin C
Kraft *et al*. 2012[15]	RCT	L-carnitine	Liquid p.o.	72	Pancreatic cancer	Oral L-carnitine (4 g) (study group) vs. placebo (control group) for 12 weeks
Mantovani *et al*. 2006[23]	Phase II study with Simon two-stage design	Polyphenol, antioxidant, pharmaco-nutritional support enriched	Tablet; liquid p.o.	39	Various primary neoplasms	All patients received integrated treatment over 4 months with high polyphenols content, antioxidants (A-lipoic acid, carbocysteine lysine salt, vitamin E, vitamin A, vitamin C), and pharmaco-nutritional support enriched with two cans per day omega-3 fatty acids, medroxyprogesterone acetate, and selective cyclooxygenase-2 inhibitor celecoxib
Hunter *et al*. 1989[24]	Prospective randomized trial	BCAA	i.v.	9	Intra-abdominal carcinoma	All patients received both conventional TPN containing 19% BCAA (AA) and isocaloric, isonitrogenous TPN containing 50% BCAA (BCAA-TPN) in random order for a minimum of 24 h
Tayek *et al*.1986[25]	RCT	BCAA	i.v.	10	Intra-abdominal carcinoma	All participants were given isonitrogenous amounts of both a conventional total parenteral nutrition (TPN) formula containing 19% BCAA a BCAA-enriched TPN formula containing 50% of the amino acids as BCAA in a random order over 2–5 days.
Yeh *et al*. 2013[26]	RCT	EE and isocal. Ethanwell contains several ingredients, including omega-3 fatty acids, glutamine, selenium, and CoQ10. Ethanzyme is an enzyme product composed of multiple probiotics and vitamins.	Liquid p.o.	68	Head and neck cancer	Patients were randomly assigned to receive either EE supplement (study group) or Isocal supplement (control group) for a 3 month period

AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BCAA, Branched-chain amino acid; BFI, Brief Pain Inventory; CO2, Carbon dioxide; ECOG, Eastern Cooperative Oncology Group performance status; EORTC, European Organization for Research and Treatment of Cancer; EORTC QLQ C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; FAACT, Functional Assessment of Cancer Therapy; FFM, Fat free mass; HMB, ß-hydroxy-ß-methylbutyrate; IL, Interleukin; i.v., intravenous; LBI, Lean body mass; MFSI-SF, Multidimensional Fatigue Symptom Inventory–Short Form; p.o., per oral; REE, Resting Energy Expenditure; NAI, Neutrophil Adhesivity Index; RCT, Randomized Controlled Trial; TNF, Tumour Necrosis Factor; TPN, Total parenteral nutrition

Table 3 (continued)

Study	Assessed tissue	Outcome measure	Narrative summary of results	Adverse effect
May *et al*. 2002[21]	Blood	Body weight; FFM	After 24 weeks of supplementation study group showed significant increase in body weight (2.27 ± 1.17 vs. 0.27 ± 1.39, $P = 0.06$) and FFM (1.6 ± 0.94 kg vs. 0.48 ± 1.08; $P < 0.05$).	None
Berk *et al*. 2008[22]		LBM	Post-treatment measurement after 8 weeks supplementation showed no significant difference in LBM.	Nausea, constipation, and/or diarrhoea; 30 patients dropped out due to side effects
Mantovani *et al*. 2010[14]	Blood	LBM, REE, MFSI-SF, IL-6, TNF-α, ECOG PS, Appetite VAS, EORTC QLQ-C30, Euro QoL EQ-5D	Post-treatment measurement after 4 months supplementation showed that group 5 was superior to all other groups concerning increase in LBM (DEXA) (43.8 ± 9.4 vs. 44.9 ± 7.7; $P = 0.015$) and appetite ($P = 0.0003$).	Diarrhoea (2 patients)
Kraft *et al*. 2012[15]	Blood	BMI, EORTC-QLQ-C30, BFI	Post-treatment measurement after 12 weeks supplementation showed increase of BMI in study group (3.4 ± 1.4% vs. −1.5 ± 1.4%, $P < 0.05$); trend towards increased overall survival in the study group (median 519 ± 50 d vs. 399 ± 43 d, P = n.s.), and reduced hospital-stay (36 ± 4 days vs. 41 ± 9 days, P = n.s.).	Nausea (8 patients), diarrhoea (2 patients), which may have been caused by concomitant chemotherapy
Mantovani *et al*. 2006[23]	Blood	Weight, LBM, Appetite, REE, Grip strength, laboratory, ECOG, EORTC QLQ-C30, Euro QL-5D, MFSI-SF	Post-treatment measurement after 4 months supplementation showed increase of body weight (55.1 ± 10 vs. 57 ± 9.8 kg, $P = 0.031$) as did LBM (38 ± 9 vs. 39.7 ± 8.7; $P = 0.024$), and appetite (5.5 ± 2.5 vs.7.0 ± 1.6; $P = 0.004$).	None
Hunter *et al*. 1989[24]	Blood, urine, breath sample	CO_2, albumin, leucine, tyrosine	After a minimum supplementation of 24 h study group showed increased flux of leucine (158.0 ± 37.2 vs. 243.5 ± 75.8 μmol/kg h; $P < 0.025$) and tyrosine (35.0 ± 84 vs. 42.6 ± 11.0 μmol/kg h; $P < 0.05$)	None
Tayek *et al*.1986[25]	Blood, urine	Protein kinetic, albumin synthesis	After 2–5 days, BCAA-enriched formula group showed significant increases in whole body protein synthesis (2.2 ± 0.2 g protein/kg BW/day vs.3.9 ± 0.3; $P < 0.005$) and leucine balance (2.5 ± 0.4 g leucine/day vs. 6.5 ± 0.6; $P < 0.001$).	None
Yeh *et al*. 2013[26]	Blood	Body weight, serum albumin, prealbumin	After 8 weeks, EE regimen significantly improved body weight compared with controls (9.0 ± 1.8 vs. −7.3 ± 3.3; $P < 0.05$) as well as serum albumin (24.7 ± 9.5 vs. 2.8 ± 6.5; $P < 0.05$) and prealbumin levels (23.6 ± 7.8 vs. 6.1 ± 14.4; $P < 0.05$).	Some patients suffered from accumulating treatment-related side effects (oral mucositis, emesis). Number of dropouts due to adverse effects not reported.

Table 4 Trials with other dietary supplements or combinations in the perioperative setting

Study	Design	Supplement	Type of application	Number of patients	Cancer type	Setting	Assessed tissue	Outcome measure	Narrative summary of results	Adverse events
Gianotti *et al*. 2002[27]	RCT	Arginine, omega-3 fatty acids, and RNA	Liquid p.o. (preoperative); per jejunal feeding (postoperative)	305	Gastrointestinal Cancer	(1) Oral supplementation for 5 days before surgery with 1 L/day of a formula enriched with arginine, omega-3 fatty acids, and RNA, with no nutritional support given after surgery; (2) Same preoperative treatment plus postoperative jejunal infusion with the same enriched formula; (3) Control group without supplementation	Blood	Incidence of postoperative infections, length of hospital stay	Supplementation significantly shortened length of hospital stay in group 1 vs. controls (11.6 ± 4.7 days vs. 14.0 ± 7.7; $P = 0.008$) and group 2 vs. controls (12.2 ± 4.1 days vs. 14.0 ± 7.7, $P = 0.03$) and less postoperative infections in the period up to 30 days after hospital discharge as measured by incidence (group 1 vs. controls 14 vs. 31, $P = 0.006$; group 2 vs. controls 16 vs. 31, $P = 0.02$)	Abdominal cramping/bloating (72 patients), diarrhoea (13 patients), vomiting (5 patients)
Stehle *et al*. 1989[29]	RCT	Glutamine and glycine	i.v.	12	Colon, rectum cancer	Study group was supplemented with a synthetic glutamine-containing dipeptide, L-alanyl-L-glutamine, alanine-N. Control group received glycine-N supplementation.	Urine, blood, biopsy of quadriceps femoris	Nitrogen balance and glutamine concentration	Cumulative nitrogen balance was significantly better in the study group on 5th post operative day (−7.1 ± 2.2 vs. −18.1 ± 1.7 g N/day; $P < 0.001$); muscle intracellular glutamine concentration was maintained in the study group, whereas it decreased in the control group (17.5 ± 1.0 vs. 12.0 ± 0.6 mmol/L, $P < 0.001$).	None
Snyderman *et al*. 1999[28]	RCT	Immune-enhancing nutritional supplement from Novartis product (Impact, Replete)	Liquid p.o.; enteral	136	Squamous cell carcinoma of the oral cavity, pharynx, larynx	Patients were divided into 4 groups: (1) supplemented diet pre-operative and post-operative, (2) supplemented diet post-operative, (3) standard diet pre-operative and post-operative, and (4) standard diet post-operative	Blood	Dietary intake, changes in weight, laboratory evaluations of nutritional status, tolerance of tube feedings, infectious and wound healing complications, and duration of hospitalization	Significant decrease in the incidence of post-operative infectious complications during hospitalization in intention to treat analysis in supplementation groups 1 + 2 vs. standard diet control groups 3 + 4 (23% vs. 45% incidence, $P = 0.04$)	None
van Bokhorst-De Van Der Schueren *et al*. 2001[30]	RCT	Arginine	Liquid per tube feeding	49	Head and neck cancer	Patients were divided into 3 groups: (1) standard pre-operative and post-operative tube feeding, (2) pre-operative enteral nutrition in which 41% of the casein was replaced by arginine and standard post-operative tube feeding, (3) no pre-operative and standard post-operative	Blood	Body weight, body composition, upper midarm circumference, skinfold thickness, muscle function, albumin at recruitment, 1, 4, and 7 days	No significant changes in nutritional status on all outcome measurements at 1, 4 and 7 days post-operatively	None

(*Continues*)

Table 4 (continued)

Study	Design	Supplement	Type of application	Number of patients	Cancer type	Setting	Assessed tissue	Outcome measure	Narrative summary of results	Adverse events
						tube feeding, study period up to 7 days post-operatively		as well as on the day of discharge		
Yamanaka *et al.* 1990[31]	RCT	BCAA	i.v.	34	Gastric cancer	Total parenteral nutrition solution supplemented with 31% BCAA vs. 21% BCAA was administered	Blood	Plasma amino acid levels were measured after administration	Administration of TPN solution supplemented with 31% BCAA was more effective to improve protein metabolism than 21% BCAA-enriched TPN	None
Buijs *et al.* 2010[32]	RCT	Arginine vs. standard perioperative enteral nutrition	Liquid per tube feeding	32	Head and neck cancer	Participants were divided into 2 groups: (1) arginine-supplemented perioperative enteral nutrition (study group) and (2) standard perioperative enteral nutrition (control group), outcome over a 10 year period	—	The primary outcome was long-term (≥10 years) survival. Secondary outcomes included the long-term appearance of loco-regional recurrence, distant metastases, and second primary tumours	Study group had a significantly better overall survival (34.8 months vs. 20.7 months; $P = 0.019$) and a better disease-specific survival (94.4 months vs. 20.8 months; $P = 0.022$)	None
Aliyazicioglu *et al.* 2013[33]	RCT	Standard and/or glutamine dipeptide and/or omega-3 fatty acids supplemented TPN	i.v.	36	Colorectal cancer	Patients were randomly divided into four groups: (1) standard TPN (control group), (2) TPN with glutamine solution (S-D), (3) TPN with omega-3 fatty acid solution (S-O), and (4) TPN with omega-3 fatty acids solution and glutamine (S-D-O). Treatments were given for 7 days after the operation	Blood	Albumin, AST, ALT, NAI, IL-8, length of stay	The length of hospital stay in supplemented groups was significantly shorter compared with control group (7.37 ± 1.77 in S-D; 7.13 ± 1.73 in S-O; 8.2 ± 1.14 in S-D-O vs. 12.48 ± 5.43; $P < 0.05$). All supplemented groups also showed significant increase (7 day postoperative) in NAI compared with control group ($P < 0.05$)	None
Braga *et al.* 2002[34]	RCT	Arginine, omega-3 fatty acids, and RNA	Liquid p.o. (preoperative); per feeding tube (postoperative)	150	Gastrointestinal cancer	(1) Post-operative standard diet; (2) For 7 days orally 1 L/day liquid diet enriched arginine, omega-3 fatty acids, and RNA for pre-operative and same as control for post-operative; (3) enriched diet pre-operative and post-operative	Blood	Postoperative complication and length of stay	Administration of supplemented diet before and after surgery shortened the pre-operative (13.2 days) and perioperative (12.0 days) length of stay compared with controls (15.3 days) ($P = 0.01$ and $P = 0.001$, respectively)	Abdominal cramps or distention (29 patients), diarrhoea (13 patients), vomiting (4 patients)
de Luis *et al.* 2013[35]	RCT	Arginine, omega-3 fatty acids	Liquid p.o.	37	Head and neck cancer	Oral consume of two (Group I) or three cans (Group II) per day of a	Blood	Albumin, prealbumin, transferrin,	After a 12 week period Group II showed significant increases in weight (69.4 ± 9.4–74.6	Nausea (2 patients)

(*Continues*)

Table 4 (continued)

Study	Design	Supplement	Type of application	Number of patients	Cancer type	Setting	Assessed tissue	Outcome measure	Narrative summary of results	Adverse events
						specially designed omega-3 fatty acids and arginine enhanced supplement for a 12 week period		lymphocytes, BMI, fat mass, FFM	± 8.9; $P < 0.05$), FFM (50.4 ± 11–53.0 ± 8.4; $P < 0.05$). Albumin, prealbumin, transferrin, and lymphocytes increased in both groups ($P < 0.05$).	

AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BCAA, Branched-chain amino acid; BMI, Body mass index; CO2, Carbon dioxide; ECOG, Eastern Cooperative Oncology Group performance status; EORTC, European Organization for Research and Treatment of Cancer; EORTC QLQ C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; FAACT, Functional Assessment of Cancer Therapy; FFM, Fat free mass; IL, Interleukin; i.v., intravenous; MFSI-SF, Multidimensional Fatigue Symptom Inventory–Short Form; p.o., per oral; REE, Resting Energy Expenditure; NAI, Neutrophil Adhesivity Index; RCT, Randomized Controlled Trial; TNF, Tumour Necrosis Factors; TPN, Total parenteral nutrition

Arginine in combination with omega-3 fatty acids and/or RNA[27,34,35] was associated with abdominal cramping, bloating, diarrhoea, nausea, and vomiting.

Discussion

A number of studies on the use of minerals, vitamins, proteins, and other supplements for the treatment of cancer cachexia were found. However, only 21 studies fulfilled the inclusion criteria and were part of this systematic review (Figure 1).

The search terms were formulated broadly (Appendix 1–3), to cover all relevant studies. The number of participants varied across studies. Most of them investigated supplementation with a combination of substances and did not provide any information on effects of single ingredients. Outcome measures across all studies included body mass, pain, muscle strength, appetite, grip strength, quality of life, and serum levels of IL-6 and TNF-α. None of the studies reported effect sizes.

The paucity of data from high quality studies on food supplements became evident in the evaluation process, even though deficiency concerning minerals,[36,37] vitamins,[38] and proteins[39] was found in several studies on cancer patients.

Minerals such as selenium or magnesium have been discussed not only for nutrition but also for immuno-function and cancer prevention; their effect on cachexia has not been investigated in detail. Thus, our literature search identified only one study on mineral supplementation examining the use of magnesium in a randomized controlled trial.[17] There was no effect of this intervention on weight loss (Table 1), so that a recommendation of magnesium to prevent weight loss in cancer is not justified.

Studies with vitamin supplements[18–20] were slightly more promising (Table 2). In one study, vitamin D supplementation showed improvement of muscle weakness in prostate cancer patients;[18] however, as measurement of muscle strength was the only outcome measure, no conclusion can be drawn concerning weight loss. With regard to vitamin C, oral and intravenous supplementation in terminal cancer patients led to improvement of several domains of quality of life such as physical and cognitive function, fatigue and appetite loss, as well as nausea.[19] A single study on vitamin E in combination with omega-3 fatty acids displayed an effect on survival.[20] Altogether, additional research on vitamin D, vitamin C, and vitamin E supplementation is recommended to give a clearer picture of possible advantages of vitamin supplementations in cancer.

Looking at studies with proteins and other dietary supplements the combination of HMB, arginine, and glutamine showed interesting results (Table 3). In one study, 32

patients gained an average of about 2 kg of body weight.[21] This study was one of three studies confirming the positive effects of this combination in a variety of diagnoses/conditions such as HIV/AIDS patients and healthy adults.[40] Another study, on a far larger sample base of around 470 cancer patients, found no significant difference with regard to LBM after 8 weeks however a strong trend in the direction of an increase in LBM as measured by both bio-impedance and skin-fold measurements.[22] In summary, the effect of the combination of HMB, arginine, and glutamine on weight gain should be investigated in further studies on cancer patients investigating time periods of several months.

With regard to perioperative supplementation arginine[27,30,32,34,35] and glutamine[29,33] in combination with other supplements displayed interesting clinical effects (length of hospital stay, infections, and overall survival) and improved protein levels (albumin and glutamine). On the other hand, mixtures containing arginine were associated with gastrointestinal side effects such as abdominal cramping, nausea, and vomiting. To date, there is not enough evidence to answer the question, whether clinical benefits of arginine supplementation in the perioperative setting justify abovementioned adverse side effects.

Carnitine deficits have been identified in 78% of patients with advanced cancer, with resurgent levels in most of these patients after carnitine supplementation.[39] One study confirmed carnitine as a promising food supplement in pancreatic cancer patients.[15] Patients with carnitine supplementation significantly gained weight with a BMI increase of over 3% on average and improved overall survival. However, of 72 enrolled patients, only 26 completed the study so that external validity of study findings is limited. In a further study,[14] results showed that L-carnitine in combination with medroxyprogesteron acetate/megestrol acetate, eicosapentaenoic acid, and thalidomide had a positive effect on LBM, fatigue, and appetite. However, L-carnitine supplementation alone did not have the same positive effect; therefore, further investigation on the influence of L-carnitine on cachexia is needed.

Two studies analysing supplementation with BCCA showed clinical benefits as measured by the albumin synthesis rate and leucine flux; however, the very small sample size did not allow for valid conclusions to be drawn. A study using a mixture of minerals, vitamins, proteins, and probiotics (EE regimen) showed improvement in body weight as well as serum albumin and prealbumin levels in head and neck cancer patients with a BMI $<$19. However, the study design does not allow for differentiation of the contribution of each of the ingredients to weight gain.

Adverse effects were reported in studies supplementing minerals,[17] vitamins,[20] and proteins.[14,15,22,26,27,34,35] In most cases, gastrointestinal side effects were reported. These effects showed mild intensity and seldom led to discontinuation or change of treatment. However, it should be noted that the dosage of supplements was controlled in abovementioned studies. As many supplements can be purchased without prescription or at the local supermarket excessive supplementation may be seen in cancer patients who are concerned about micronutrient deficiencies and there may be a risk of potentially harmful self-medication. A survey among breast cancer patients showed the potential for excessive vitamin/mineral use among one-third of respondents.[41] Even though in studies on humans to date no major adverse events due to food supplementation have been reported, in animal studies, supplementation with N-acetylcysteine and vitamin E accelerated lung cancer progression in mice.[42]

Regarding limitations of our systematic review, expanding the search to additional databases or to non-English literature might have resulted in more hits. However, it seems improbably that there is a significantly larger body of evidence not identified by our search strategy.

In summary, studies with a greater number of participants are urgently needed, although problems with recruitment and high attrition have been identified in many other reviews in advanced cancer or palliative care. Similarly, the positive effects of some studies with combination therapies lend support to the necessity of additional research on the individual components. In order to prioritize research ambitions and provide useful guidance for cancer and palliative care, studies should focus on the effect of food supplements on nutritional status and cachexia-related symptoms in patients and cancer types most affected by cachexia.

Conclusions

Following the GRADE methodology, no positive recommendation could be expressed for the use of minerals, vitamins, proteins, or other supplements in cancer patients. On the other hand, no serious adverse effects have been associated with dietary supplementation. Further research is needed to identify the efficacy and safety of these supplements to be able to give clear evidence-based recommendations.

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Appendix 1. CENTRAL search strategy.
Appendix 2. MEDLINE search strategy.
Appendix 3. PsycINFO search strategy.

Online supplementary material

Supporting information is available at Journal of Cachexia, Sarcopenia and Muscle online.

Conflict of interest

None declared.

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