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Nutrition in oncology: The case of micronutrients (Review)

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Abstract. In the course of cancer disease, many oncological patients develop tumor-associated malnutrition characterized by an insufficient supply of macro- and micronutrients. The inadequate nutritional status and the cancer anorexia-cachexia syndrome related to it are clinically relevant, as the response to antineoplastic measures, such as radiation and chemotherapy, is diminished, their side effects aggravated and the patient's quality of life and prognosis negatively affected. Therefore, the supportive nutrition care of oncological patients is of central importance. In this context, vitamins, minerals and long-chain ω-3 fatty acids are becoming more and more relevant in oncology although the benefit of such supplements is discussed controversially. Starting from a description of the etiopathogenesis and the pathophysiological consequences of cancer-associated malnutrition, the present study provides an overview of the importance of micronutrients for oncological patients. In the case of reduced food intake and/or inappropriate food choice the use of a multi-vitamin-multimineral supplement administered in physiological doses, i.e. nutrient quantities approximately corresponding to the recommended daily allowances, can be generally recommended. However, to enhance postoperative wound healing, it seems that cancer patients require higher amounts of micronutrients than healthy individuals. Because vitamin D deficiency is highly prevalent in oncological patients, improvement of vitamin D status is of special interest.

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1. Introduction

According to current estimates, about 11 million people develop malignant tumors worldwide every year. Among the most frequent cancer diseases are neoplasias of the lung, colon and rectum and, depending on the patient's gender, neoplasias of the prostate and mammary gland (1). Due to the age-depending cancer incidence and the ageing population, the number of new cancer cases is expected to double until the year 2030 (2). Both epidemiological and experimental-mechanistic studies confirm that eating habits and/or individual nutrition factors fundamentally modify the risk of developing epithelial tumor diseases (3-7).

Whereas the benefit of a healthy eating strategy in the sense of 'chemoprevention' (8-11) has been established scientifically for some time (6,7), additional measures of nutrition care also are of great significance for patients suffering from a manifest cancer disease (12-16). This is due to the fact that many cancer patients develop a tumor-associated malnutrition characterized by an insufficient supply of macro- and micronutrients (17-31). The inadequate nutrition status and the cancer anorexia-cachexia syndrome combined with it (15,32-34) are clinically relevant because they not only diminish the response to antineoplastic measures, such as radiation and chemotherapy (35,36), but also aggravate their side effects and have a negative impact on the patient's quality of life and prognosis (14,37-43). Thus, an adequate nutritional intervention can have a beneficial influence on the progress of the disease and the patient's condition. Against this background it is evident that a supportive nutrition therapy should be an integral part of cancer care (44-46). In addition to a sufficient supply of energy substrates, vitamins and minerals as well as long-chain ω-3 fatty acids are becoming more and more interesting (31,47-56), although the therapeutic benefit of such supplements is the subject of a controversial discussion, especially in respect

Table I. Frequency of malnutrition defined by a disease-related weight loss depending on tumor localization.

Type of tumor	Proportion of patients (%)
Pancreatic carcinoma	83
Gastric carcinoma	83
Esophageal carcinoma	79
Carcinomas of the head and neck	72
Colorectal carcinoma	55-60
Pulmonary carcinoma	50-66
Prostate carcinoma	56
Mammary carcinoma	10-35

Source, Laviano and Meguid (68).

of supplements with high concentrations of antioxidants like the vitamins C and E and the trace element selenium (57-66).

Starting from a description of the etiopathogenesis and the pathophysiological consequences of cancer-associated malnutrition, the present study provide an overview of the relevance of micronutrients to oncological patients. Following van Ommen *et al* (67), the term of 'micronutrients' includes both vitamins and mineral substances as well as ω-3 fatty acids.

2. Tumor-associated malnutrition – etiopathogenesis and pathophysiological consequences

Malnutrition, primarily characterized by a rapid weight loss, is a typical finding in patients suffering from cancer (19-26). Depending on the type and localization of the tumor and the stage of the disease, significant malnutrition is observed in 30-90% of the tumor patients, and many patients have nutrition deficits already before the therapy begins (19,20,41). Malnutrition is particularly severe in patients with a tumor of the gastrointestinal tract (Table I).

Tumor-associated malnutrition is of multifactorial origin (Fig. 1, right side of the picture) and initially due to a reduced substrate and energy supply which has itself various causes related to the cancer disease. They include (12,15): i) neuropsychological-dysregulation of the hunger-satiation feeling characterized by the development of anorexia found in 15-40% of the tumor patients (69), for which, in addition to taste and smell abnormalities (70-73) and disease-related depressive symptoms (74), mainly the cytokine-mediated dysfunction of the hypothalamic neurochemistry is made responsible (33,75-77). Thus, it is assumed that various cytokines, such as interleukin-6 (IL-6) and tumor-necrosis factor α (TNF-α) which are secreted in large amounts by the tumor itself but, due to the tumor disease, also by the host organism, inhibit the neuropeptide Y (NPY) signal cascade in the lateral hypothalamus and increase the expression and release of pro-opiomelanocortin (POMC) in the diobasal hypothalamus. Both effects act as an anorectic signal and reduce the hunger feeling and therefore the food intake (33); ii) mechanical-disturbed food intake, e.g. due to tumors in the oral cavity and oesophagus (78); iii) physiological-impaired nutrient digestion and/or absorption due to tumors in the gastrointestinal tract (78); and iv) iatrogenic-disturbed nutrient utilization as a result of antineoplastic therapy, associated with a consecutive nutrient deficit. In general, the risk of malnutrition rises when antineoplastic procedures are initiated (15,24,36). In particular radiation and chemotherapy, and to an ever larger extent the combined chemo-readiotherapy, is associated with a number of side effects (such as stomatitis, enteritis and mucositis) (79,80) which, as a secondary effect, may affect the patient's food selection as well as nutrient absorption and nutrient utilization (24,81-83, Tables II and III).

Malnutrition is associated with and aggravated by a higher metabolic turnover rate observed in many cancer patients caused by certain substances released by the tumor itself, such as the tumor peptides proteolysis inducing factor (PIF) and lipid mobilizing factor (LMF), and the cytokines IL-6 and TNF-α mentioned above. As anorexogenic mediators both classes of compounds lead to a number of changes in the intermediary macronutrient metabolism (Fig. 1, left side). They include among others (33,88-92): i) increase in whole body protein turn-over (93) with elevated protein catabolism combined with persistent degradation of muscle protein (94). At the molecular level, these changes are mainly induced by the proteolysis inducing factor (PIF), a sulphated glycoprotein which activates the enzyme phospholipase A_2 in the muscle cells leading to an increased release of arachidonic acid (AA) from the cell membranes. AA is then partly transformed into 15-hydroxyeicosatetraenic acid by 15-lipogenase. Hydroxyeicosatetraenic acid activates NADPH oxidase and thus the formation of reactive oxygen species (superoxide radicals; ($^{\bullet}O2^{-}$) causing the upregulation of the inducible transcription factor NF-κB which induces the expression of the ubiquitin-proteasome system (95-98). This ATP-depending proteolysis complex contains, as an essential component, multicatalytic proteases which finally catalyze the hydrolytic protein degradation in the myocytes (for an overview of the ubiquitin-proteasome system see ref. 90); and ii) mobilization of peripheral fat and decrease of whole body lipid (99) as a result of increased lipolysis (100) and higher lipid oxidation (101). The lipid mobilizing factor (LMF) and zinc α-glycoprotein (ZAG) could be identified as the principal mediators of these changes. Both activate the hormone-sensitive lipase via the cAMP pathway and thus the hydrolytic release of fatty acids from the adipocytes (102,103).

In combination with the reduced nutrient intake and/or absorption mentioned above, the catabolic changes in the metabolism finally lead to the development of cancer cachexia characterized by a drastic weight loss-especially loss of substantial body mass ('wasting'), and systemic inflammation (104). The latter is associated with an increased formation of reactive oxygen species (ROS) which could be detected in cancer patients (53).

Tumor-associated malnutrition and the tumor cachexia related to it not only diminish the response to antineoplastic therapy (35,36) and aggravate the side effects of tumor therapy (35,36,108,110), but also affect the patient's quality of life (14), a fact of clinical relevance. Especially the finding that

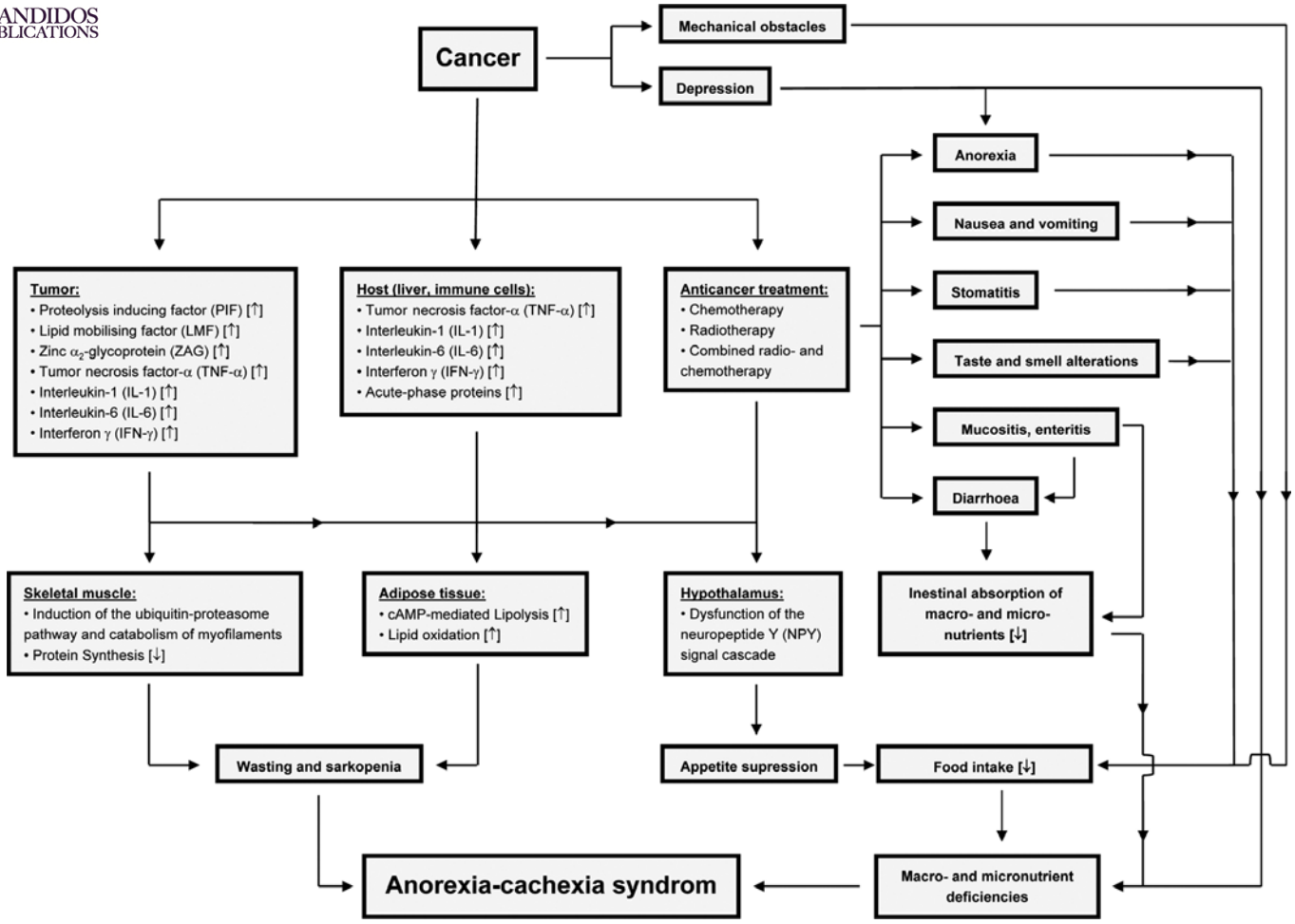

Figure 1. Multifactorial genesis of tumor-associated malnutrition and cachexia (based on the sources of refs. 15,34,89,105-107).

malnourished cancer patients have an elevated morbidity and mortality risk is clinically relevant (41,42,111-118). Besides sepsis, tumor cachexia still is the most frequent cause of death of cancer patients (13).

3. Tumor-associated deficit of micronutrients – pathophysiological consequences and therapeutic options with micronutrient supplements

As Fig. 1 shows, the malnutrition of many cancer patients is not limited to macronutrients, but the supply of various vitamins and minerals also is often inadequate. In general, a deficient micronutrient supply can be assumed for all cancer patients whose energy uptake amounts to <60% of the daily requirements for more than 10 days and who, according to the ESPEN Guidelines, must be considered inadequately supplied with food (13). This especially applies if, under chemo and radiation therapy, they rapidly lose, i.e. use up, micronutrients due to vomiting and diarrhea (84).

In fact, the status of vitamins C (119-121), D (122-124) and E (125) and of some B vitamins (126-128) is significantly lowered in many tumor patients compared with healthy individuals and/or the defined cut-off values found in the literature. For example, the vitamin C plasma levels found in some cancer patients are so low that they suffer from scurvy-like symptoms (129,130). Also a significantly decreased concentration of the trace elements selenium and zinc was found in the serum of cancer patients (31,51,131,132), and cases of severe deficiency symptoms (133) were described. The insufficient supply of antioxidant micronutrients of many cancer patients can also be seen in the fact that their oxidative stress markers are often increased (120,134-136). The problem is aggravated by the falling vitamins A (137) and E (137,138-140) blood levels under radiation therapy.

Such a micronutrient deficit caused by the cancer disease is of importance in many respects: first, it compromises wound healing, so that there is a higher risk of complications after surgical interventions (141,142). Secondly, a less than optimum supply of micronutrients, especially of some B vitamins, is associated with a higher risk of depressive symptoms (143,144). Thirdly, even a moderate micronutrient deficit will compromise the immune competence of the organism (145,146), as immune cells, due to their high proliferation rate, have an increased nutrient need. Therefore, the inadequate supply of vitamins and minerals has a negative effect on the immune defense of cancer patients. In this context, especially the trace elements zinc and selenium

Table II. Diet-related side effects of chemotherapy.

Adverse effects	Precipitating cancer treatments	Nutrition effects
Nausea and vomiting	Most chemotherapy agents	Can significantly reduce food intake and cause dehydration
Mucositis (in the upper gastrointestinal tract: gingivitis, pharyngitis and oesophagitis)	Antimetabolites, cytotoxic antibiotics	Inflammation of mucosal epithelium cells of the gastro-intestinal tract
Diarrhea	5-Fluorouracil (5-FU), irinotecan, hydroxyurea, methotrexate (MTX), dactinomycin	Intestinal loss of vitamins and electrolytes, disturbances of the acid-base-homeostasis
Stomatitis	Bleomycin, dactinomycin, doxorubicin (DOX), 5-fluorouracil (5-FU), methotrexate (MTX)	Sore mouth can significantly affect food intake/cause food aversions
Taste and smell alterations	Carboplatin (CBP), cisplatin, cyclo-phosphamide, doxorubicin (DOX), 5-fluorouracil (5-FU), methotrexate (MTX)	Reports of food tasting metallic, like cardboard or sandpaper, too salty, sweet, sour, or bitter, or having no taste

Modified according to Grant and Kravits (84) including O'Brien *et al* (85) and Naidu *et al* (86).

and vitamins E and C are of relevance. Table IV provides an overview of the immunobiological significance of selected vitamins and trace elements (following 146) ↓, reduced; (↓) possibly reduced; ↑ increased; (↑), possibly increased; →, no effect; n.d., no data; C, controversial findings.

Against this background it is clearly evident that measures of nutrition medicine for cancer patients are important and necessary. Besides an adequate intake of energy-building substrates, an optimum supply of micronutrients is also required (27-30,147). Therefore, in recent years the administration of micronutrient supplements to cancer patients has gained growing interest (31,47-51,53,54,56). From the dietetic-therapeutic point of view, such substances can perform the following functions (148): i) compensation of a nutrient deficit induced by the cancer disease itself and/or the antineoplastic therapy with the aim of improving the patient's nutritional status; and ii) specific supplementation for dietetic-therapeutic purposes aiming less at the supply of nutrients, rather at taking a beneficial influence on the course of the disease.

4. Micronutrient supplementation in the supportive nutrition care of tumor patients – compensating a nutrient deficit

As explained in Section 3, many cancer patients have a multiple nutrient deficit. The risk of a less than optimum supply is particularly high if the food intake (based on the energy supply) amounts to <60% of the required level over an extended period (>10 days). In such cases it is often impossible to meet the nutrient requirements, not to mention the replenishment of empty nutrient storage sites of cancer patients just by the usual diet. The problem is made more difficult by the restricted dietary patterns of many cancer patients due to their food aversion (73,78,149). Therefore, using micronutrient supplements can make sense in these cases (147,150). Clinical studies have actually shown that the nutritional status of tumor patients can be improved by giving them vitamins and mineral substances (31,51).

The question for the dose of vitamins and minerals that is useful and safe from the nutrition physiology point of view is more difficult to answer. As the degree of malnutrition (19), and thus the micronutrient deficit, differs in cancer patients depending on the tumor localization, the tumor stage and the type of antineoplastic therapy, the amount of micronutrients needed for dietetic care will have to vary from case to case. In general, for enteral feeding of all tumor patients a daily uptake amounting to the respective Recommended Dietary Allowances (RDA) (13) is recommended, an advice that can also be made with regard to the corresponding multivitamin-multimineral supplements (59,147).

Referring to their antioxidant compound content (vitamins C, E and selenium), the question whether supplying such substances during chemo and/or radiation therapy can be considered safe (58,59,62,64-66), has repeatedly been the subject of a controversial discussion. Micronutrients with an antioxidant effect actually have the potential for capturing reactive oxygen species (ROS). In tumor biology this is sometimes considered a problem, as the tumor-destroying effect of chemo or radiation therapy is partly due to an increased formation of ROS (151,152). It is therefore possible that the adjuvant administration of antioxidants during chemo and radiation therapy will weaken the therapeutic effect and thus worsen the tumor patient's prognosis.

SPANDIDOS PUBLICATIONS Diet-related side effects of radiation therapy.

Radiated body region	Acute effects	Late effects
Central nervous system	Nausea	
	Vomiting	
Otolaryngological region	Swallowing disorders	Ulcer
	Dry mouth	Dry mouth
	Mucositis	Bone necrosis
	Anorexia	Caries/sensitive tooth necks
	Taste and smell alterations	Reduced/lacking sense of taste
Thorax (lung, mediastinium, oesophagus)	Swallowing disorders	Esophageal fibrosis
	Inappetence	Esophageal stenosis
	Nausea	Esophageal perforation
		Esophageal fistula
Abdomen and pelvis	Anorexia	Ulcer
	Nausea	Diarrhea/malabsorption
	Vomiting	Bleeding
	Diarrhea	Chronic enteritis/colitis
	Acute enteritis	Stricture/obstruction
	Acute colitis	Fistula/perforation
	Acute proctitis	Ureter stenosis
	Sphincter insufficiency	Renal failure
	Acute cystitis	

Modified according to 87.

In addition to cell culture studies and animal experiments, interventional studies were made with tumor patients based on these considerations with the aim of finding an answer to the question whether antioxidant supplementation would actually have a negative impact on the effectiveness of chemo or radiation therapy. Meanwhile a large number of survey studies (60-66,153-159) have been published, some of a systematic nature (56,57), summarizing and evaluating the findings. In this context, two contradictory positions have developed expressed by two different views (147) maintaining that the administration of antioxidant supplements (in higher doses) as an adjuvant to chemo and/or radiation therapy: i) is not associated with any negative effects on the tumor-destroying therapy; and ii) is associated with a weakening of the tumor-destroying therapy.

Thus, the adjuvant supply during chemo and radiation therapy is recommended (60,64) on the one hand, and there is the opposite opinion warning against such a measure (65,66) on the other. These divergent views can be explained, among other things, by the fact that the influence of an antioxidant supplementation on the effect of chemo or radiation therapy seems to depend on a number of factors (147): i) degree to which radicals are formed by the chemotherapeutic agent and in how far the chemotherapeutic effect depends on the potential formation of free radicals; ii) type of reactive oxygen compounds formed by the chemotherapeutic agent; iii) dose of the chemotherapeutic agent and concentration of the active oxygen species; iv) type of antioxidant; v) dose of antioxidant; and vi) time between application of the antioxidant and chemotherapy.

After evaluating the available data on the effect of antioxidant supplementation during chemo or radiation therapy, the American Institute for Cancer Research (AICR) arrives at the conclusion that patients under chemo or radiation therapy should abstain from taking vitamins or mineral substances containing more antioxidants in the daily amount than corresponds to the Upper Limits of Safe Intake (vitamin C, 2000 mg/day, vitamin E, 250 mg/day tocopherol equivalents, and selenium 400 μg/day) (160). In general, says the AICR, taking dietary supplements during chemo or radiation therapy is to be considered safe as long as such supplements contain amounts of vitamins and mineral substances that are in the range of the recommended daily allowance according to the RDA recommendations (59).

5. Micronutrient supplementation in the supportive nutrition care of tumor patients – influencing the disease symptoms

Besides aiming at compensating the micronutrient deficit caused by the tumor disease, such supplements can also be given in order to influence the course of the disease in a

Table IV. Immunological significance of selected vitamins and trace elements adapted from Ströhle and Hahn (146).

Micronutrient	Biochemical function	Immunological function	Effect on immune competence
Vitamin A	• As retinoids it regulates transcription of various genes whose corresponding proteins are involved in the control of cell growth and cell differentiation • As retinyl ester, carrier of mannose and involved in glycoprotein synthesis	• Essential factor for the integrity of skin and mucous membranes that act as antigen barrier • Essential for humoral and cellular immune response	*Deficiency:* • Weakening the skin-mucosa barrier and increasing infection risk • Proliferation and cytotoxicity of T-lymphocytes ↓ • Antigen-specific response ↓ • Proinflammatory effect (TNF-α synthesis ↑) • Change in TH1:TH2 ratio in favor of TH1 *Supplementation (physiological doses)* • Phagocytosis ↑ • Synthesis of interferon-γ, TNF-α ↓ • Antibody formation ↑ *Supplementation (non-physiological doses)* • Antigen-specific response ↓
Vitamin E	• Antioxidant defense • Signal transduction	• Reduces immune suppressive effect of free radicals in respiratory burst • Modulation of eicosanoid formation via inhbition of cyclooxigenase and lipid oxygenase with resulting anti-inflammatory activity • Essential for humoral and cellular immune response	*Deficiency* • Antigen-specific response ↓ • Proliferation and cytotoxicity of T-lymphocytes ↓ • Phagocytosis ↓ *Supplementation (physiological doses)* • T-cell proliferation ↑ • Favorable effect on $CD4^+$:$CD8^+$ quotient • Oxidative stress ↓ • Th1 activity ↑ *Supplementation (non-physiological doses)* • Antigen-specific response ↓
Vitamin B_6	• Coenzyme in porphyrin and amino acid metabolism, involved in nucleic acid and protein synthesis • Modulates effect of steroid hormones	• Essential factor for antibody and cytokine synthesis	*Deficiency* • Lymphocyte maturation and proliferation ↓ • T-lymphocyte activity ↓ • Antibody formation ↓ • Interleukin-2 synthesis of T-helper cells ↓ *Supplementation (physiological doses)* • Lymphocyte proliferation ↑ • Interleukin-2 synthesis of T-helper cells ↓

 Continued.

Micronutrient	Biochemical function	Immunological function	Effect on immune competence
Folic acid	• Coenzyme in the metabolism of amino acids, purins, pyrimidines and cholin; thus involved in the nucleic acid and protein synthesis • Epigenetic modification of DNA via methylation	• Essential factor for the growth of rapidly proliferating immune cells • Essential factor for antibody and cytokine synthesis	*Deficiency:* • Thymus weight ↓ • Neutrophil activity↓ • Cytotoxicity of T-lymphocytes ↓ • Antibody formation ↓ • Lymphocyte proliferation ↓ • Activity of natural killer cells ↓ *Supplementation (physiological doses):* • Lymphocyte proliferation ↑ • Cytotoxicity of natural killer cells ↑
Vitamin B_{12}	• Coenzyme in the metabolism of homocystein, odd-numbered fatty acids and branched-chain amino acids	• Closely related to folic acid metabolism, essential for the growth of immune cells and antibody and cytokine synthesis	*Deficiency:* •Neutrophil activity ↓ • Activity of natural killer cells ↓
Iron	• As a component of hemoglobin and myoglobin involved in erythrocytic oxygen transport and oxygen storage in the muscles • Component of metalloenzymes, e.g. dioxygenases and monooxygenases, involved in eicosanoid, carnitine, collagen and neurotransmitter synthesis • Component of hemenzymes, e.g. guanylate cyclase, NO-synthase, peroxidase and catalase, involved in signal transduction and antioxidant defense	• Essential factor for maturation, differentiation and proliferation of lymphocytes • Essential factor for cytokine synthesis • As a component of NADPH oxireductase and myeloperoxidase involved in the formation of antimicrobial hypochloride	*Deficiency:* • Secretion of interferon-γ, TNF-α and interleukin 2 ↓ • Activity of natural killer cells ↓ • T-cell proliferation ↓ • Bactericidal activity of macrophages ↓ *Iron overloading:* • Activity of natural killer cells ↓ • Quotient $CD4^+$:$CD8^+$ ↓
Zinc	• Integral component, i.e. effector, of over 150 enzymes of all 6 enzyme classes, involved in carbohydrate, lipid, amino acid and nucleic acid metabolism • Site-specific antioxidant • Component of transcription factors, regulates gene expression	• Essential factor of thymulin synthesis, needed for T-cell activity (cytotoxicity, etc.) • Essential factor for cytokine synthesis • Essential factor for the growth of all rapidly proliferating immune cells • Protects immune cells against oxidative damage • Essential factor for the integrity of skin and mucous membranes acting as antigen barrier	*Deficiency*: • Interferon-γ and interleukin 2 synthesis ↓ • Activity of natural killer cells ↓ • Macrophage activity↓ (phagocytosis ↓; bactericidal effect ↓, chemotaxis ↓) • T-cell activity ↓ • Thymus atrophy *Supplementation (physiological doses):* • Phagocytosis ↑ • Activity of natural killer cells ↑ • Antibody formation ↑ *Supplementation (non-physiological doses)* • Lymphocyte proliferation ↑ • Interferon-γ synthesis ↓ T-cell activity ↓
Selenium	• Component of glutathion peroxidase, involved in the degradation of peroxides, e.g. hydrogen peroxide	• Essential factor for lymphocyte activity	*Deficiency:* • Proinflammatory eicosanoid synthesis ↑ • Antibody formation ↓

Table IV. Continued.

Micronutrient	Biochemical function	Immunological function	Effect on immune competence
Selenium	• Component of deiodases, involved in the transformation of thyroxine (T4) to triiodine thyronine • Component of thioreductases, involved in the redox metabolism	• Protects immune cells against oxidative damage	• Lymphocyte proliferation ↓ • Cytotoxicity of immune competent cells ↓ *Supplementation (physiological doses):* • Interferon-γ synthesis • Th1 response ↑ • T-lymphocyte proliferation ↑ • Cytotoxicity of natural killer cells ↑

beneficial way: i) to support wound healing; ii) to counteract tumor cachexia; and iii) in the longer term to improve the patient's quality of life and prognosis.

Supporting wound healing. Among the multiple ways of treating tumors, surgical procedures play an important role, both as a primary measure and after neoadjuvant, volume-reducing chemo or radiation therapy. Rapid wound healing of the surgical site free of complications is often crucial to the success of any subsequent therapy. Disturbed wound healing and resulting infections not only impair the patient's quality of life but also delay further therapeutic measures (141,142).

Both wound closure and tissue regeneration are processes that depend on an adequate supply of micronutrients. Vitamins A, C, E and B_6 in particular, but also the trace elements zinc, manganese and copper, as enzyme cofactors, are involved in biochemical-physiological processes that are directly related to would healing (Table V).

One micronutrient that is given great attention both experimentally and clinically is vitamin C (ascorbic acid). As an essential cofactor for the dioxygenases prolyl 4-, prolyl 3- and lysyl hydroxylase, ascorbic acid is relevant to the structure and function of collagen, as the ascorbate dependent dioxygenases cause the cotranslational hydroxylation of proline and lysine residues in the procollagen (165,166). Although it has been known for a long time that the postoperative need for vitamin C is higher than normal (167,168), the question for the optimum vitamin C supply for wound healing in humans has so far not been definitely answered. Based on the results of an interventional study made by Taylor *et al* (169), a vitamin C supply of 1000 mg/day can be recommended to post-surgical patients (164), an amount that is also recommended for the optimization of wound healing (163). For the other micronutrients shown in Table V there are no reliable data from studies in humans so that the recommended doses mentioned for them can only be considered approximate values.

The pronounced synergy effects of the individual micronutrients are of clinical relevance. They help us understand why the use of single highly dosed substances often remains ineffective whereas nutrient combinations of multiple composition can produce clinically relevant effects (164).

Controlling cachexia. Starting from the recognition that various anorexogenic mediators, such as PIF, cytokines (e.g. IL-6 and TNF-α) and ROS, are central to the genesis of tumor cachexia, micronutrient supplements offer nutritional care two basic approaches. They include the administration of: i) antioxidants (vitamins C and E, N-acetylcystein, α-liponic acid) (54-56,170-172); and ii) fish oils (173-175).

Whereas the findings on the anticachectic effects of an antioxidant therapy are still in the experimental stage for the most part, and therefore not dealt with any further in this study, there are abundant preclinical and clinical data on the subject of 'fish oils and tumor cachexia' The fish oil components relevant in this context are the long-chain ω-3 fatty acids eicosapentaenic acid (EPA, C20:5ω-3) and docosahexaenic acid (DHA, C22:6ω-3). Humans are capable of synthesising both fatty acids from α-linolenic acid (ALA, C18:3ω-3) in a multistage conversion process, which primarily takes place in the endoplasmic reticulum of liver cells (176). However, the synthesis of EPA and DHA from ALA is extremely slow and low yielding (177). It is estimated that an intake of approximately 20 g pure ALA is necessary to obtain 1 g EPA (178). The synthesis of DHA in humans appears to be more complicated than was long thought, since it is clear that another pathway also exists (179). According to the alternative pathway, docosapentanoic acid (C22:5ω-3) is elongated to become tetracosapentanoic acid (C24:5ω-3) followed by a Δ6 desaturation. The next reaction step occurs after transfer of the fatty acid to peroxisomes, where a specific ß-oxidation shortens the chain to a C22 product. The complexity of this conversion may be another reason for its ineffectiveness.

With respect to cancer cachexia, EPA display mainly two direct biochemical effects: inhibition of the TNF-α and the PIF signalling pathway, whereby in both cases the inhibition of the NF-κB system, and thus finally the downregulation of

Significance of selected micronutrients for wound healing (compiled according to 161-164).

Micronutrient	Biochemical function	Physiological function for wound healing	Recommended daily dose
Vitamin C (ascorbic acid)	Cofactor of prolyl-3/prolyl-4 oxidase and lysyl hydroxylase (prolyl-6 oxidase)	Essential for postranslational hydroxylation of procollagen and thus for the synthesis of collagen and its interlinkage in the connective tissue	500-2000 mg[a]
Vitamin A	*Retinoids:* Element of transcription factor, regulation of gene expression and synthesis of proteins involved in the control of cell growth and cell differentiation *Retinyl ester:* Carrier of mannose, involved in glycoprotein synthesis	Essential for epithelial-dermal integrity	10000 IU[b]
Vitamin B_6 (pyridoxine)	*Pyridoxal phosphate (PALP):* Cofactor of amino transferases	Essential for connective tissue protein synthesis	10-15 mg[a]
Folic acid	*Tetrahydrofolate (THF):* Cofactor of C-1 metabolism (transfer of methyl, methylene and formyl residues), involved in amino acid, purine and pyrimidine synthesis	Essential for connective tissue protein synthesis	0.4-1.0 mg[a]
Zinc	Cofactor of prolyl-4 oxidase and matrix-metalloproteases	Essential for postranslational procollagen hydroxylation, and thus for synthesis of collagen and its crosslinking in connective tissues Essential for keratocyte migration into the wound area	4-10 mg[a] (in case of low initial plasma values)
Copper	Cofactor of prolyl-6 oxidase (lysyl hydroxylase); inducer of endothelial growth factor (EGF)	Essential for postranslational procollagen hydroxylation, and thus for synthesis of collagen and its crosslinking in connective tissues Essential for angiogenesis in the wound area	1-2 mg[a]

[a]According to data of Demling (163); [b]according to data of Kurmann and Burrowes (164).

the ubiquitin-proteasome system, seems to play a key role (96-98,180,181) (Fig. 2).

Based on animal experiments which confirm the anti-cachectic effects of an ω-3 fatty acid supplementation, a number of prospective observational and interventional studies with cancer patients have meanwhile been made and evaluated (173,174). A review of 17 such studies by Colomer *et al* (173) led to the following results: i) enteral supplements containing long-chain ω-3 fatty acids are of benefit (increased weight and appetite) in patients with advanced cancer and weight loss, and are recommended in patients with tumors of the upper digestive tract and pancreas; ii) the recommended dose is 1.5-2.0 g per day long-chain ω-3 fatty acids (EPA); and iii) there is low incidence of adverse side effects, so there is no limitation with respect to duration of supplementation.

Quality of life and prognosis. The relevance of micronutrients as part of the supportive nutritional care of cancer patients is confirmed not least by the results of studies showing that the intake of micronutrient supplements can improve both the quality of life and the prognosis of tumor patients (38-40). Thus, in an observational study with lung cancer patients the risk of dying was 20% lower in the patients

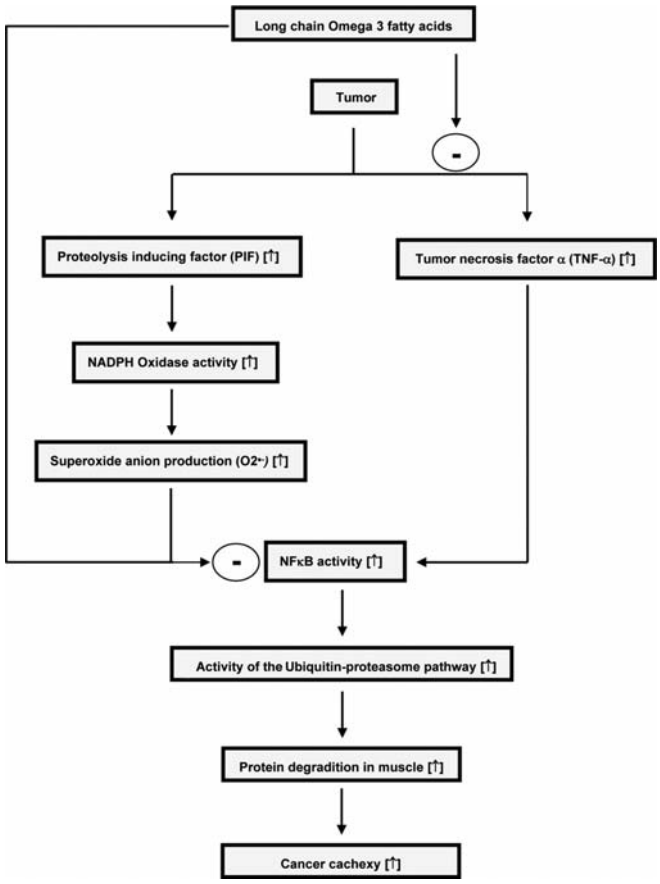

Figure 2. Anticachectic effect of long-chain ω-3 fatty acids. '-', down-regulate).

using supplements vs. those not using supplements (95% confidence interval (CI): 0.44, 0.65; p<0.01). The mean survival time of the patients taking micronutrient supplements was 4.3 years, whereas it was only 2 years for the patients who did not take any. Moreover, in this study using a micronutrient supplement was associated with an improvement in the quality of life (Lung Cancer Symptom Scale) (mean difference in score of 3 (95% CI: 0.8, 5.1; p<0.01); and after adjusting for related variables, there remained a trend in favor of vitamin/mineral use mean difference 1.8 (95% CI: 0.2, 3.9; p=0.08) (39). In this context, the result of a randomized, unblinded, clinical trial with long-chain ω-3 fatty acids is of relevance which when giving the patients fish oil demonstrated a significantly (p<0.001) longer survival time of patients with generalized solid tumors (47). There also are first indications showing that ω-3 fatty acids may improve the cellular absorption of various chemotherapeutic agents and thus support the effectiveness of antineoplastic therapy (50). In addition, the results of current prospective observational studies indicate that the subject of 'vitamin D supply and prognosis of tumor patients' may become more important in the field of oncology in the future. For instance, the plasma level of 25-hydroxyvitamin D_3 proved to be an independent predictor for the survival of patients with breast cancer (182) and patients with colorectal carcinoma (183,184). In view of the data on the vitamin D deficit of tumor patients (122-124) presented in Section 3, these finding deserve special attention.

6. Summary and recommendations

In the course or their disease, many cancer patients develop tumor-associated malnutrition which, among other things, is characterized by a micronutrient deficit. In practice, it is not always possible in such special circumstances to counteract this condition in an optimum way by the diet, i.e. the conventional food selection. Often the situation is made more difficult by the limited dietary pattern of tumor patients which may lead to a very one-sided nutrition. Therefore, it is not surprising that the use of nutrient supplements, among them especially vitamins and mineral substances, is widespread among cancer patients (185,186). However, the interest in micronutrient supplements is not restricted to the group of users. On the contrary, the use of vitamins, mineral substances and long-chain ω-3 fatty acids is also gaining a growing, though controversial, interest in oncology (51-66).

Based on the above, our findings can be summarized for practical purposes in the following way: i) in view of the restricted dietary pattern of tumor patients, the use of a multivitamin-multimineral supplement in physiological doses, i.e. nutrient amounts that approximately equal the recommended daily allowance, is a useful (147,150) and safe (59) measure. This also applies to oncological patients during chemo and radiation therapy (59); ii) in general, the use of single high-dose micronutrients should be avoided. An exception is vitamin D. Depending on the basal 25-OH-D_3 plasma level, the vitamin D supply should amount to 1800-4000 IU/day (45-100 μg/day of cholecalciferol) in order to reach the desirable plasma concentration of >75 nmoll/l in most oncological patients (187,188); iii) to improve postoperative wound healing, an increased micronutrient supply is recommended [500-2000 mg/day vitamin C, 3 mg/day vitamin A, 10-15 mg/day vitamin B6, 0.4-1.0 mg/day folic acid, 4-10 mg/day (in case of initially low plasma levels 40 mg/day) zinc, 1-2 mg/day copper] (163,164); and iv) on the basis of a cost-benefit analysis, the tentative adminstration of long-chain ω-3 fatty acids (1.5-2.0 g per day) to patients with weight loss and tumor cachexia is to be recommended (173).

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