Micronutrients and the Immune System
Contents

4 The immune system – a complex system needs optimum support
6 What is orthomolecular nutritional medicine?
7 Micronutrients – nutritional support for the immune system
14 Oxidative stress – the threat posed by free radicals
14 Formation of free radicals
16 Which people need a particularly large supply of antioxidant micronutrients?
18 Increased need for micronutrients in case of illness
18 Micronutrients as nutritional support
20 Dietary treatment of infectious diseases
24 Keeping inflammation under control
24 Micronutrients and wound healing
28 Allergies, asthma and COPD
31 Reducing the cancer risk – supporting tumor therapy
35 Micronutrients in oncology
40 Literature
The immune system – a complex system needs optimum support

The immune system is one of the most complicated and complex networks in the human body’s organ systems (Fig. 1). Its principal functions include the defense against infections and tumors and the involvement in tissue regeneration.

Like all body systems, the immune system is based on biochemical metabolic processes and cellular mechanisms that depend on the external supply of energy and micronutrients. As the immune system, compared with other systems of the human body, mainly consists of rapidly proliferating cells, it is particularly sensitive to an inadequate supply of micronutrients. Before the clinical or subclinical symptoms of an insufficient micronutrient supply can be recognized, the functional impairment of the immune response may already be observed.

The immune system has an especially high turnover rate in chronic diseases or infections. Immune cells must be activated rapidly in the right place at the right time. This is why the immune system is particularly vulnerable to a lack of micronutrients in such cases.

Any shortage in the supply of micronutrients to the immune system should therefore be prevented by a regular, appropriate intake. This is where orthomolecular nutritional medicine comes in. The organism is provided with an additional quantity of certain vitamins and trace elements in the right composition and dosage.
This brochure gives you an impression of the importance of micronutrients for the immune system. It also shows what orthomolecular nutritional medicine (Fig. 2) can do to support the treatment of diseases. With orthomolecular nutritional medicine, doctors have an effective opportunity to recommend to their patients a supplementary nutritive therapy above and beyond the established methods. Many ill people feel the need to actively contribute to the healing process themselves in addition to the therapeutic measures taken by their doctor.

What is orthomolecular nutritional medicine?
“Orthomolecular nutritional medicine is the preservation of good health and treatment of disease by varying the concentrations in the human body of substances that are normally present in the body, and that are required for good health.” (Linus Pauling)65

The functions of orthodox medicine and orthomolecular medicine

Orthodox medicine
- Protecting and restoring health

Orthomolecular medicine
- Protecting and restoring the body’s functions (e.g. immune defense and regeneration) as well as supporting the treatment of diseases

Table 1. Features of important micronutrients related to the immune system30,31,36,53,74,80,84

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Vitamin A</th>
<th>Vitamin C</th>
<th>Vitamin E</th>
<th>Vitamin D3</th>
<th>Zinc</th>
<th>Beta-carotene</th>
<th>Selenium, copper, manganese</th>
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<td>Proliferation and activation of lymphocytes</td>
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<td>Activation of macrophages</td>
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<td>Phagocytosis</td>
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<td>Proinflammatory cytokines (TNFα, IL-1β, IL-6)</td>
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Micronutrients – nutritional support for the immune system

We have known for decades that malnutrition or undernourishment may impair the function of the immune system. But even in a generally adequate nutritional situation, an increased need for vitamins and trace elements, often going unrecognized, may considerably weaken the immune system (Table 1). Micronutrients, with their nutritional and physiological properties and characteristics, may influence the immune system in many different ways.

Thus, for instance, a lack of vitamin A can impair the formation of antibodies against certain bacterial antigens. In animal experiments, fewer granulocytes, B cells and natural killer cells were generated.12 Moreover, a lack of vitamin A will aggravate inflammatory reactions, and experimental studies have shown that this vitamin can inhibit various types of inflammatory reactions.16
Animal experiments and studies in humans suggest that a vitamin B6 deficiency will have a negative effect on the humoral as well as the cell-mediated immune response. Thus, for instance, a vitamin B6 deficiency will change the differentiation and maturation of lymphocytes, reduce the delayed-type hypersensitivity reaction and may impair antibody production. In a recent study it was shown that a vitamin B6 intake above the recommended RDA* (2.1–2.7 mg per day), however, will significantly increase lymphocyte proliferation and may therefore have a beneficial influence on the immune response.

The physiological function of various cell types of the immune system depends on an adequate supply of vitamin C. As vitamin C has a strong antioxidant capacity, it protects many types of tissue. Vitamin C plays an important part in the immune function, the modulation of the body’s resistance against infection pathogens and it can reduce the risk, severity and duration of infectious diseases and accelerate recovery.

A particularly high vitamin C concentration is found in neutrophilic granulocytes where the vitamin protects the intracellular compartments, such as the phagocytic cell membrane, against the damaging effect of oxygen radicals. Moreover, the proliferation of T lymphocytes can be enhanced by vitamin C supplementation, and the activity of leukocytes and natural killer cells can be improved.

In addition, in several case-control studies it was found that a high vitamin C intake will reduce the risk of gastric cancer. This is supposed to be due to the neutralization of the carcinogenic nitrosamines by this vitamin, among other reasons.

Vitamin C is also important for the healing process, as it boosts the function of specific immune defense cells (Fig. 4). Besides, vitamin C enhances the iron absorption in the intestines and thus influences iron transport and iron storage.

Vitamin E has an antioxidant effect and thus protects the tissues and blood cells. Adequate vitamin E levels are essential for the function of the immune cells. Vitamin E improves both the humoral and cellular immune response as well as phagocytosis. Many studies have shown that vitamin E has a beneficial effect on the immune function of older people. Thus, a correlation was found between the plasma vitamin E level and the course of a delayed-type hypersensitivity reaction (type-IV reaction) on the skin and the response to a hepatitis-B vaccination. In addition, various clinical trials and animal studies indicate that supplementary vitamin E intake can improve resistance in old age, especially to viral infections of the upper respiratory tract including influenza.

There are probably two mechanisms that are responsible for the immunomodulatory effects of vitamin E: on the one hand, vitamin E has an indirect effect by reducing the formation of immunosuppressive factors, such as PGE2, and on the other it promotes cell division and the interleukin-2 production of naive T cells.

Antioxidants are complementary to each other in their effects. For example, vitamin E, which oxidizes itself and becomes ineffective when oxygen radicals are inactivated, can be reduced again by vitamin C and can thus be "recycled" to its active version. Vitamin C in its turn is reduced by the selenium-containing glutathion peroxidase.

* RDA: recommended dietary allowance
The last link in the chain is the enzyme superoxide dismutase (SOD) which needs zinc as a cofactor.\(^7\)

**Vitamin A** has many important characteristics that are essential to maintaining the basic functions of the human body: it regulates cell division and tissue growth. Moreover, it strengthens the barrier function of the skin and mucosa and plays an essential part in adaptive immunity as it is needed for the development of helper T cells and B cells.\(^12\)

The carotenoid **beta-carotene**, as **provitamin A**, is a vitamin A precursor. As an antioxidant it is able to scavenge aggressive oxygen radicals, it protects the body cells against their damaging effect, and it helps prevent cancer.\(^80\)

**Carotenoids** can, for instance, contribute to the protection against the detrimental oxidative impact of ozone. Among other functions, ozone leads to the formation of free radicals that attack the lung tissues and causes a significant reduction in plasma carotenoids. Carotenoid intake can increase the carotenoid concentration in the plasma and lung macrophages and thus counteract their depletion under an ozone load.\(^76\) In addition, beta-carotene enhances the immune defense and weakens the skin reaction in patients with light dermatosis.

The trace element **selenium**, as a component of the glutathion peroxidases and thioredoxin reductases, which both have an antioxidant effect, protects the tissues against oxidative stress. Thus, glutathion peroxidase, for instance, is very important for the degradation of lipid peroxide. Moreover, more than 20 selenoproteins have meanwhile been identified that are involved in the cell and thyroid metabolism and the immunofunction.\(^9\)

By influencing phagocytosis, selenium helps eliminate harmful microorganisms.\(^9\) It is an important factor for many functions of the immune system (Table 2)\(^9\) and thus also contributes to the immune defense against degenerated cells. In many studies it could be shown that selenium intake is associated with a reduced cancer risk (e.g. cancer of the intestines and prostate gland).\(^31,46\)

**Zinc** is an important cofactor of more than 300 metalloenzymes that would be unable to function without zinc.\(^26\) It promotes the development and integrity of the immune system (Fig. 3, Table 2).\(^26\) Zinc, for instance, is essential for the activation of thymoduline (thymic hormone) which regulates lymphocyte maturation.\(^26\) Zinc also seems to play a role in cytokine activity, as the biologic activity of IL-1, 2, 3, 4 and 6, IFN-β and TNF-α is impaired in people with a zinc deficiency.\(^26\) A lack of this micronutrient leads to a higher susceptibility to infections and a decline in T lymphocytes (cytotoxic T cells, helper T cells), reduces the activity of natural killer cells and impairs the phagocytosis of macrophages and neutrophils.\(^63\)

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**Fig. 3. Functions of zinc for immune defense.**\(^10,26,43\)
Iron deficiency is one of the most frequent nutritional deficiencies. Iron is an essential component of the enzyme myeloperoxidase which granulocytes require for phagocytosis. In children with a lack of iron the number of immunocompetent T cells is drastically reduced and the susceptibility to infections increased. A recent study with older women has shown that iron deficiency is associated with a disorder of the cell-mediated and congenital immunity. Besides, iron is essential to the transport of oxygen because every hemoglobin molecule consists of 4 subunits with one hem-group each containing a central iron atom. As a cofactor of peroxidases and catalases, iron helps eliminate detrimental peroxides.

Copper as a component of many metalloproteins is involved in various metabolic reactions. They include the respiratory chain (cytochrome-C-oxidase), the antioxidant defense (superoxide dismutase, coerulo plasmin), the synthesis and degradation of catecholamine (dopamine-β hydroxylase, monoamine oxidase), and the formation of connective tissue (lysoxidase). As this trace element has an important position in the iron metabolism, it plays a role in the hemoglobin synthesis and thus the transport of oxygen.

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<th>Table 2. Immune function with deficiency of certain trace elements</th>
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<td>Anergy*</td>
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<td>Thymus atrophy</td>
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<td>Lymphocytes</td>
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<td>Helper T cell activity</td>
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<td>Antibody formation</td>
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<td>Phagocytosis</td>
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<td>Activity of natural killer cells</td>
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</tbody>
</table>

* anergy = lack of response for an antigen  + occurs  - not specified  ▼ decreased

Fig. 4. Role of micronutrients in relevant metabolic processes

Micronutrients involved in relevant metabolic processes
Oxidative stress – the threat posed by free radicals

Besides noxious substances, bacteria and viruses, the formation of free radicals also threatens the organism. Free radicals react very easily with other molecules through unpaired electrons and thus have a detrimental effect on tissues and cells (Fig. 5). They interfere with the correct pllication of important proteins, oxidize the lipid membranes of the cells and affect the ideo-plasm. The sum of all these effects is called oxidative stress.

Formation of free radicals

• Free radicals can develop either endogenically as metabolic products, especially in inflammatory processes such as chronic respiratory tract diseases (asthma, COPD*) and hepatic diseases (hepatitis)
• Or they are of exogenic origin generated by environmental pollutants, ozone, high-energy radiation (e.g. X-rays or sunlight), certain drugs, and smoking

To protect itself against the free radicals and their detrimental effects, the organism can make use of two antioxidant systems (Table 4):
• Antioxidant enzymes which are formed by the body itself; an adequate supply of the trace elements selenium, copper, iron, zinc and manganese is needed for their synthesis, or
• Non-enzymatic antioxidants which have to be ingested through food; these include in particular vitamins C and E as well as phytonutrients such as carotenoids and bioflavonoids

To ensure that the body has an adequate supply of antioxidant systems at all times, the micronutrients required for this purpose, such as vitamins C and E, phytonutrients (carotenoids and bioflavonoids) and trace elements (selenium, zinc, manganese and copper), must be taken regularly (Fig. 6).

A study by Cheng et al. 2001 showed that a short-term supply of vitamins and minerals (for 16 weeks) improved the antioxidant status and increased the activity of antioxidant enzymes. The resistance of the red blood cells to peroxidation processes was also significantly higher.

Table 3. Sources of important micronutrients

<table>
<thead>
<tr>
<th>Micronutrients</th>
<th>Sources</th>
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<tbody>
<tr>
<td>Vitamin B₆ (pyridoxine)</td>
<td>Meat, fish, vegetables (Brussels sprouts, avocado)</td>
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<tr>
<td>Vitamin B₁₂ (cyanocobalamin)</td>
<td>Meat, liver, kidney, milk, fish</td>
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<tr>
<td>Folic acid</td>
<td>Green vegetables, giblets</td>
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<tr>
<td>Vitamin K₁</td>
<td>Green vegetables (curly kale, broccoli, etc.)</td>
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<tr>
<td>Vitamin D₃</td>
<td>Fish, milk</td>
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<tr>
<td>Vitamin C</td>
<td>Fruit, vegetables (paprika, broccoli, etc.)</td>
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<tr>
<td>Vitamin A</td>
<td>Liver, carrots, tuna, cheese</td>
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<tr>
<td>Vitamin E</td>
<td>Vegetable and fish oils, nuts, eggs, giblets</td>
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<tr>
<td>Carotenoids</td>
<td>Vegetables and fruit</td>
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<tr>
<td>Bioflavonoids</td>
<td>Vegetables and fruit</td>
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<tr>
<td>Selenium</td>
<td>Seafish, meat, eggs, cereals</td>
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<tr>
<td>Zinc</td>
<td>Meat, fish, milk</td>
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<tr>
<td>Copper</td>
<td>Liver, nuts</td>
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<tr>
<td>Manganese</td>
<td>Cereals</td>
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<td>Iron</td>
<td>Meat</td>
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<tr>
<td>Iodine</td>
<td>Seafish</td>
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</table>

* COPD: chronic obstructive pulmonary disease
Detrimental effects of free radicals

DNA damage

DNA double helix

Radical

Denaturation of proteins

Protein in pleated-sheet structure

Radical

Lipid peroxidation

Lipid cell membrane

Radical

Fig. 5. Effects of free radicals on DNA, proteins and lipids

Which people need a particularly large supply of antioxidant micronutrients?8,35,48,49,56,62,69,73,79,81,84

- People with acute or chronic infections
- People with chronic illnesses, such as respiratory tract diseases (asthma, COPD), or hepatic diseases (hepatitis)
- Elderly people
- Top-performance athletes
- People who are exposed to special environmental pollutants (e.g. smog, ozone)
- People who smoke and/or regularly consume alcohol
- People with metabolic disorders
- People who are exposed to intense sunlight
- People who mingle with many other people and are therefore exposed to an elevated risk of infection

Table 4. Features of antioxidant systems

<table>
<thead>
<tr>
<th>Non-enzymatic antioxidants</th>
<th>Trace elements in antioxidant enzymes</th>
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<tbody>
<tr>
<td>Vitamin C</td>
<td>Selenium</td>
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<tr>
<td>Water-soluble, reaction with toxic oxygen radicals, prevents the penetration of free radicals in the lipid phase</td>
<td>Central component of the antioxidant enzyme glutathione peroxidase, important for the protection of erythrocytes</td>
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<tr>
<td>Vitamin E</td>
<td>Iron</td>
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<tr>
<td>Fat-soluble, especially in cell membranes, prevents oxidation of unsaturated fatty acids</td>
<td>Component of catalases, a group of antioxidant enzymes</td>
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<tr>
<td>Carotenoids</td>
<td>Zinc, manganese, copper</td>
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<tr>
<td>Fat-soluble, especially effective against singlet oxygen, protect DNA against radical chain reaction (provitamin A)</td>
<td>Components of superoxide dismutases having antioxidant efficacy</td>
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<td>Bioflavonoids</td>
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<td>Antioxidants from vegetables</td>
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</table>

Antioxidants control free radicals

Vitamin E

Bioflavonoids

Selenium

Copper

Zinc

Manganese

Fig. 6. Antioxidants as radical scavengers
Increased need for micronutrients in case of illness

In certain illnesses the need for micronutrients may increase, for instance in people with infectious or chronic diseases who have to take a certain medication regularly. Often this increased need for micronutrients cannot be covered with normal eating habits. You would have to eat 2 kg of oranges in order to ingest 950 mg of vitamin C. 350 ml of thistle oil contains 150 mg of vitamin E. For a dose of 5 mg of mixed carotenoids you would have to eat 50 g of carrots and 50 g of tomatoes. A large proportion of the population therefore does not receive a sufficient supply of micronutrients. For example, the intake of vitamin D3, folic acid, pantothenic acid and iodine is much lower than the nutrient supply reference levels of the DGE. According to the recent DGE nutrition report, for instance, 45% of women and 45.5% of men do not reach the DGE reference level for folic acid. Moreover, many foods lose important micronutrients over a long storage period or when they are prepared.

Micronutrients as nutritional support

Micronutrients help support the defense system and maintain good health. In prospective studies, for instance, it was shown that the supplementation of combinations of vitamins and trace elements can reduce the risk of infection. But even patients who are already ill will benefit from an increased supply because micronutrient supplementation can:

- Cover the higher demand due to an acute disease or a certain medication (Table 5)
- Contribute to stimulating the immune system and wound healing, and also support drug therapy
- Mitigate drug side effects
- Have a beneficial influence on the antibody reaction after an influenza vaccination

Table 5. Vitamin supply affected by pharmaceuticals

<table>
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<tr>
<th>Pharmaceuticals</th>
<th>Vitamin A</th>
<th>Vitamin B1</th>
<th>Vitamin B2</th>
<th>Nicotinamide</th>
<th>Vitamin B6</th>
<th>Folic acid</th>
<th>C</th>
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<td>Amiodarone</td>
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a Colestyramine  b Fibrates  c Methotrexate
Dietary treatment of infectious diseases

Vitamins and trace elements are essential for the functions of the immune system. Therefore, the need for them greatly increases in people with infections. Many studies have shown that the optimum supply of these substances can support the treatment of infections and the defense against pathogens. Moreover, antioxidants scavenge harmful free radicals of which a higher number is produced during infectious diseases and can thus have a beneficial influence on the course of the disease.

In an interventional trial, the intake of a micronutrient combination (Orthomol® Immun) could improve general health and strengthen the immune defense. Thus, after taking the micronutrients for four months, vitality improved by 39.5%, the quality of life by 29.6%, and the general health was 31.7% better than before. Within the reference values the blood test demonstrated a significant multiplication of immunoactive cells and a significant improvement in the immune status. Thanks to the micronutrient combination, the absence rate due to illness could be reduced significantly by 75.6% compared to the previous year (p<0.001, Fig. 7). In the control group, the number of days lost due to illness increased. Common colds also dropped by 48.6% compared to the previous year.19

In a placebo-controlled double-blind trial the preventive effect of a micronutrient supplementation on a group of subjects aged >65 years (Fig. 8) was investigated. In the observation period (1 year) the test group subjects' immune status improved considerably (increase in T and NK cells with higher activity of these immune cells, more interleukin-2 production and enhanced antibody response). In comparison with the placebo group, the number of days of illness due to infections could be reduced by more than 50%.10

In another study of the same design, the 12-month administration of a micronutrient combination to a group of subjects aged 50 to 65 led to a significantly higher antibody response after influenza vaccination and a decline in the number of influenza infections.20 Jain et al. (2002)44 also showed that the 12-month administration of a micronutrient combination led to a significant reduction in the number of days of illness due to respi-
AIDS is also associated with a malfunction of the immune system and malnutrition. The levels of vitamins A, B6, B12, C and E, beta-carotene and selenium are often lowered in this group of patients. In some studies the administration of vitamins C and E reduced the oxidative stress and the viral load. In addition, an in-vitro study has shown that vitamin C inhibits the proliferation of HIV-infected cells (14±2 days vs. 29±4 days in the placebo group; p=0.03).

Fawzi et al. (2004) demonstrated that the nutritive effect of multivitamins will slow down the progression of an HIV infection. Moreover, the risk of developing HIV-associated symptoms could be markedly reduced. These symptoms include oral thrush, ulcers or aphthae, difficulty in swallowing, nausea and vomiting, exhaustion and skin rashes. Taking the multivitamin product also led to much higher CD4+ and CD8+ cell counts. As a result of the significant reduction in the viral load (by 0.18 Log10) the time to the outbreak of AIDS or death could be prolonged by about 30%.

Chronic diseases or infections, such as pancreatitis or viral hepatitis, are associated with high oxidative stress. Accordingly, in two prospective double-blind trials a high vitamin E intake to support the treatment of hepatitis B and C infections led to an improvement in the following clinical parameters: ALT*, AST** and/or only ALT*. Chronic pancreatitis could also be improved by supplementary intake of antioxidants (vitamin E, beta-carotene, selenium). Another study showed that patients with chronic active hepatitis, cirrhosis of the liver and liver cell carcinoma have low serum levels of the antioxidant vitamin C.

In the study by Langkamp-Henken et al. (2004), older people who had taken a micronutrient combination for 183 days had a considerably better immune function than the placebo group and recovered from respiratory tract infections much faster. They also formed more antibodies after an influenza vaccination.

Athletes have an increased risk of infection, mainly due to the oxidative stress under great physical exertion. Also, the body’s own production of corticosteroids, which depresses the activity of the immune system, increases under high-level physical strain. The preventive benefit of antioxidants was clearly demonstrated in placebo-controlled studies. Thus, the infection rate of athletes declined by about 50% after they had taken vitamin C.

In several clinical trials it was shown that taking vitamin A markedly reduces the morbidity and mortality involved in various infectious diseases, among them measles, pneumonia, malaria and HIV infection. Animal studies have shown that a deficiency in selenium and vitamin E may increase the virulence of viruses. The assumed mode of action is probably the genetic mutation of the pathogen caused by the excess amount of free radicals. People infected with HIV and AIDS patients have an increased need for micronutrients. These patients display elevated oxidative stress.

In the study by Barringer et al. (2003), a 12-month supplementation with a micronutrient combination reduced the general risk of infection significantly by 41%.

In the study by Fawzi et al. (2004), older people who had taken a micronutrient combination for 183 days had a considerably better immune function than the placebo group and recovered from respiratory tract infections much faster. They also formed more antibodies after an influenza vaccination.

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AIDS is also associated with a malfunction of the immune system and malnutrition. The levels of vitamins A, B6, B12, C and E, beta-carotene and selenium are often lowered in this group of patients. The supplementation of these micronutrients has an immunomodulating effect and strengthens the cellular defense. In some studies the administration of vitamins C and E reduced the oxidative stress and the viral load. In addition, an in-vitro study has shown that vitamin C inhibits the proliferation of HIV-infected cells (14±2 days vs. 29±4 days in the placebo group; p=0.03).

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* ALT: Alanine Aminotransferase
** AST: Aspartate Aminotransferase
Keeping inflammation under control

The body reacts to detrimental irritations by releasing a large number of mediators. In this complex reaction, the various proinflammatory cytokines and free radicals become fully effective. A very strong defensive reaction may cause extended tissue damage and/or chronicity of inflammatory processes. Endogenic antioxidants, such as glutathion, and exogenic antioxidants, such as vitamins C and E, phytonutrients (carotenoids and bioflavonoids) as well as trace elements (zinc, selenium and copper) can regulate cytokine production and protect the tissues against the damage caused by free radicals. Therefore, micronutrient supply is one of the factors influencing the outcome of inflammatory processes.34

Patients with chronic inflammation, such as hepatitis, pancreatitis or COPD, also suffer from increased oxidative stress and therefore benefit from an extra supply of antioxidants as well.3,8,69,78,79,81

Micronutrients and wound healing

Patients with pressure ulcers show signs of a systemic inflammatory reaction. Thus, they demonstrate an elevated level of oxidative stress and reduced serum concentrations of important antioxidants. This should be taken into account in the treatment of pressure ulcers.25 In general, smaller or larger wound areas after accidents, inflammatory processes or surgery do not heal as fast as would be possible under optimum circumstances. The cause may be a micronutrient deficiency. As the immune system is under an immense strain during the phase of wound healing (Fig. 9), it is important to ensure an adequate supply of vitamins and trace elements.
Vitamins C, B<sub>6</sub>, copper and manganese are essential to the collagen synthesis because, as enzyme cofactors, they are responsible for cross-linking the collagen fibers. Vitamin A promotes the differentiation of epithelial cells. Vitamin E protects the lipids of the cell membrane against oxidation and thus reduces the oxidative stress caused by injuries. Selenium, a trace element and a building block of antioxidant enzymes, also counteracts oxidative stress.<sup>57</sup>

The B vitamins, especially pantothenic acid, promote wound healing by stimulating the synthesis of fatty acids and collagen.<sup>57</sup>

A lack of zinc, on the other hand, will disturb wound healing.<sup>1,57</sup> Zinc, as a component of various metalloenzymes, is absolutely necessary for protein biosynthesis and cell division and thus accelerates wound healing. In addition, zinc stimulates the lymphocytes and activates the macrophages.<sup>74</sup>

The iron of the hemoglobin is important for the transport of oxygen to the wound area.<sup>14</sup> It also supports collagen synthesis.<sup>14</sup> Thus, the optimum supply of micronutrients is a crucial factor for rapid wound closure and tissue regeneration (Table 6).

### Table 6. Role of important micronutrients for wound healing

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Sources</th>
<th>Features and characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Liver, milk, eggs</td>
<td>Supports cell division and cell differentiation, stimulation of epithelial cells</td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>Yellow and orange fruits and dark green leafy vegetables</td>
<td>High antioxidant potential</td>
</tr>
<tr>
<td>B vitamins</td>
<td>Meat, cereals, milk, green vegetables, fish, potatoes</td>
<td>Components of enzymes of the energy metabolism, collagen synthesis (vitamin B&lt;sub&gt;6&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Citrus fruits, vegetables, potatoes</td>
<td>Collagen formation, enhancement of immune defense, radical scavenger, contributes to the regeneration of vitamin E</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Oils, nuts, eggs, giblets</td>
<td>Enhancement of immune defense, radical scavenger</td>
</tr>
<tr>
<td>Vitamin K&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Milk, giblets, green vegetables</td>
<td>Stimulation of blood clotting</td>
</tr>
<tr>
<td>Copper</td>
<td>Liver, nuts, wholemeal products, legumes</td>
<td>Cofactor of enzymes which cross-link collagen and elastin</td>
</tr>
<tr>
<td>Zinc</td>
<td>All foods of animal origin</td>
<td>Increase of cytokine formation, stimulation of lymphocytes, activation of macrophages, radical scavenger</td>
</tr>
<tr>
<td>Selenium</td>
<td>Seafood, eggs, meat, cereals</td>
<td>Radical scavenger</td>
</tr>
</tbody>
</table>
Allergies, asthma and COPD

In an allergy the reactivity of the immune system is pathologically increased. The contact with the antigen triggering the allergy will lead to an excessive formation of IgE-antibodies and/or, with a time delay, to the release of lymphokines from specifically sensitized T lymphocytes. Histamine released from mast cells causes typical symptoms, such as swelling, urtication and itching.

In animal experiments it was found that high vitamin E doses can suppress allergic symptoms. Moreover, vitamin C acts as a histamine antagonist. People with a low vitamin C level have elevated plasma histamine concentrations.

In patients with a histamine intolerance foods like red wine or cheese that contain this biogenic amine will cause headaches and other allergic symptoms. It is suggested that this may be due to a reduced activity of diaminoxidase, an enzyme that degrades histamine. Besides a low-histamine diet, a larger supply of vitamin B6 will improve the symptoms because vitamin B6 increases the diaminoxidase activity.

A number of studies have shown that patients with chronic inflammation of the respiratory tract (asthma and COPD) suffer from elevated oxidative stress. In asthma and COPD patients the impaired pulmonary function is reflected by an imbalance in oxidant and antioxidant substances. In the study by Tug et al. (2004) the oxidative stress of COPD patients rose during an acute episode and remained high also in the subsequent stable phase. The rise in oxidative stress was reflected by an increase in lipid peroxidation, i.e. elevated malondialdehyde (MDA) levels, a reduced glutathion peroxidase activity, and a low vitamin C level. Interestingly, the vitamin A and E serum concentrations declined in the acute phase of a COPD attack (Fig. 10). In the study by Kelly et al. (1999) asthma patients also had lower vitamin C and E concentrations, larger quantities of oxidized glutathione in the respiratory tract secretion and elevated oxidative stress. Compared with healthy controls, COPD patients had greatly increased MDA values, and thus higher oxidative stress, after physical exertion. After taking vitamins E and C for one month, the same COPD patients no longer displayed increased MDA levels after physical exertion, and the maximum physical load period was significantly longer. Thus, antioxidants can mitigate the detrimental effects of oxidative stress if patients with a chronic pulmonary disease take nutritive measures.

Ocht-Balcom (2006) was able to show that a similarly high intake of antioxidants ingested through food by patients with chronic respiratory tract diseases obviously leads to lower plasma levels than it does in healthy subjects.

![COPD and increased oxidative stress](image-url)

**Fig. 10.** Mean serum level of stress markers and antioxidant vitamins

* p<0.01: COPD exacerbation vs. stable phase, COPD exacerbation vs. control
Reducing the cancer risk – supporting tumor therapy

Vitamins and other micronutrients are not a cure for malignant tumor diseases. Under no circumstances must they take the place of the appropriate therapeutic methods of orthodox medicine, such as surgery, chemotherapy or radiation therapy. But, combined with other elements of a healthy lifestyle, they can contribute to primary and secondary prevention and in many cases actively support medical therapy. The reports over the last decades dealing with the beneficial effects especially of antioxidant micronutrients were repeatedly confirmed by controlled studies over the past few years.

Besides environmental factors and genetic disposition, lifestyle and nutrition are important factors for the development of cancer. According to some estimates, the Western diet is responsible for about 40% of all tumor diseases. It is a high-fat diet deficient in dietary fibers, polyunsaturated fatty acids, vitamins and trace elements. The insufficient consumption of fruit and vegetables is associated with a higher cancer risk probably connected with the resulting inadequate supply of vitamins and trace elements. A deficit of iron, zinc, folic acid, vitamins B₆, B₁₂, and C can damage the DNA and thus promote the development of cancer.

In addition, a large number of epidemiological studies were able to show a correlation between the lack of certain antioxidants, trace elements (such as selenium) or vitamins and the risk of developing various types of cancer. Thus, a deficit of vitamins A, C and E or carotenoids was correlated to the cancer incidence just as frequently as an undersupply of vitamins D₃, B₀₆, B₁₂, and folic acid (Table 7). Numerous studies have demonstrated that vitamin C helps prevent cancer of the bladder, breast, cervix and colon and a number of other tumors. People with a deficiency of vitamin D were found to have an elevated colon cancer risk.
Other studies with people at risk showed a significantly lower risk for certain tumor diseases when micronutrient consumption was high:

- A nutrition intervention study in Linxian (China) including 30,000 subjects showed that the daily intake of beta-carotene, vitamin E and selenium could considerably reduce the esophageal and gastric cancer risk which is particularly high in that part of the world. The mortality of both types of cancer declined by about 20%, the number of cases by 10%. Total mortality and the mortality due to cerebrovascular diseases were also lower.

- The daily consumption of a combination of vitamins A, C and E led to a lower recurrence rate after the removal of colorectal polyps.

- A recent meta-analysis of 14 studies including a total of 351,077 subjects (thereof 8,816 cancer patients and 342,261 healthy subjects) proved that the daily intake of 1,000 IU (= 25 μg) of vitamin D reduced the colon cancer risk by 50%.

- Over an average period of 14.8 years, Larsson et al. (2005) observed 61,433 Swedish women aged between 40 and 76 who did not show any signs of cancer at the beginning of the trial. When the study started (in 1987-90) and in 1997 the vitamin B6 quantity ingested through food and the alcohol consumption were determined by means of a questionnaire. After an average period of 14.8 years, 805 colon cancer cases were identified. The long-term intake of vitamin B6 was significant and inversely correlated to the colon cancer risk.

- A prospective cohort study (Nurses’ Health Study) found that folic acid counteracts the elevated breast cancer risk resulting from regular alcohol consumption. Women who consumed alcohol had a 50% lower relative breast cancer risk if they took at least 600 μg of folic acid daily. This high amount of folic acid was mostly taken in the form of multivitamin products.

- Other studies have shown that a high folic acid intake and/or high folic acid blood levels are associated with a low relapse risk of colorectal adenoma (reduction of 34% and 39%, respectively). A low homocysteine level and a high vitamin B6 intake were also associated with a lower relapse rate.

- In a recent pilot study with patients suffering from precancerous laryngeal leukoplakia who were given folic acid (3 x 5 mg per day) over a 6-month period, a beneficial effect was noted. In 72% of the treated patients the precancerous leukoplakia shrank by at least 50% or even disappeared completely. According to the investigating scientists, folic acid products could therefore be used for the secondary prevention of such risks.

People who are suffering from cancer have increased oxidative stress and low antioxidant concentrations. This was found, among others, for breast, cervix and colon cancer. The authors assume that oxidative stress has an influence on cancer development. Such patients therefore have an elevated need for antioxidants.
Thus, the nutritive supplementation of antioxidants can counteract oxidative damage resulting, for instance, from increased lipid oxidation.\textsuperscript{75,90} Thanks to their nutritive and physiological characteristics,\textsuperscript{68} antioxidants are able to:

- Increase the effectiveness of chemotherapy, radiation therapy and hyperthermia
- Reduce the expression of oncogenes in cancer cells
- Induce differentiation of cancer cells
- Strengthen the body’s own defenses
- Mitigate the toxicity of cancer therapy

Chemotherapy and radiation therapy make use of the difference between normal tissue and uncontrollably growing tumors in order to destroy the cancer cells as selectively as possible. Many studies have shown that micronutrients:

- Differ in their effect on cancer and normal cells
   In cultured rodent and human cancer cells, the treatment with antioxidant vitamins (\textit{vitamins C and E}) and \textit{beta-carotene} induces cell differentiation and inhibits cell growth. The underlying mechanisms are complex. Vitamins A and E, for instance, enhance growth-inhibiting signals (e.g. by protein kinase C inhibition) and lead to a reduction in oncogene expression (e.g. c-myc and H-ras). Moreover, vitamin E increases the production and release of TGF-β, a growth inhibitor, and reduces the phosphorylation and activity of transcription factor E2F which plays a central role in cell proliferation.\textsuperscript{68} \textit{Beta-carotene}, for instance, inhibits the growth of cell lines from human prostate gland carcinomas.\textsuperscript{87} In vitro \textit{vitamins D, E and K} as well as \textit{beta-carotene} induce in many tumor cell lines the “programmed cell death” (apoptosis), whereas this effect is not observed in healthy cells.\textsuperscript{23} The most powerful proapoptotic effect is reached by a combination of vitamins C and E.\textsuperscript{23}

- Support the effect of standard therapies
   Initial results show that individual antioxidant vitamins or a combination of several \textit{vitamins} enhance the growth-inhibiting effect of radiation therapy, chemotherapy and hyperthermal treatment.\textsuperscript{68} A large number of cell and animal studies indicate that \textit{vitamins A, C and E} and \textit{beta-carotene} increase the growth-inhibiting effect of many cytostatic drugs (such as cisplatin) or radiation therapy.\textsuperscript{24,68}
Moreover, the synergies between vitamin A and tamoxifen increase the apoptosis of cultivated breast cancer cells. Prasad et al. (1994) also found that the growth of human melanoma cells can be inhibited much more effectively by chemotherapeutic drugs, such as cisplatin, as well as by decarbazine and tamoxifen, when vitamin C alone, a combination of beta-carotene with a vitamin E and vitamin A derivative, and the combination of vitamin C, beta-carotene and the vitamin E and A derivative was taken. The combined administration of several vitamins had the most powerful effect. These micronutrients support each other functionally. Thus, for instance, vitamin C restores the antioxidant function of vitamin E.

**Counteract many adverse effects of cancer therapy**

In animal experiments vitamins C and E reduce the toxic effect of the antineoplastic drugs doxorubicin and bleomycin on healthy cells. Healthy body cells seem to accumulate far lower antioxidant levels than cancer cells, so that healthy cells are protected against the growth inhibiting effects of standard cancer therapy, whereas the high antioxidant levels in the cancer cells trigger the growth inhibiting signals and differentiations mentioned. Thanks to this selective action, chemotherapy can be made less toxic.

**Diminish the side effects of the therapy**

Chemotherapy and radiation therapy are a considerable strain on the immune system. Tumor surgery that may be required also burdens the immune system. Micronutrients are then needed, e.g. for wound healing. At the same time, the intake and resorption of nutrients may be impaired by lack of appetite, vomiting and diarrhea. Therefore, tumor treatment should be supported by an adequate supply of micronutrients helping the immune system to recover, strengthening the defense against infections and promoting wound healing (Fig. 11).
### Table 7. Sources of micronutrients and their features and characteristics, especially related to cancer diseases

<table>
<thead>
<tr>
<th>Micronutrients</th>
<th>Sources</th>
<th>Features and characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B₁ (thiamin)</td>
<td>Pork, cereals</td>
<td>Optimization of cell functions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Important for the energy metabolism</td>
</tr>
<tr>
<td>Vitamin B₂ (riboflavin)</td>
<td>Cheese, meat, fish</td>
<td>Optimization of cell functions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Important for the energy metabolism</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>Meat, fish, cheese, eggs</td>
<td>Optimization of cell functions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Important for the energy metabolism</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>Meat, fish, mushrooms, cereals</td>
<td>Important for the energy metabolism</td>
</tr>
<tr>
<td>Vitamin B₆ (pyridoxine)</td>
<td>Meat, fish, vegetables (Brussels sprouts, avocado)</td>
<td>Optimization of cell functions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Important for the energy metabolism</td>
</tr>
<tr>
<td>Vitamin B₁₂ (cyanocobalamin)</td>
<td>Meat, liver, kidney, milk, fish</td>
<td>Important for blood formation</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Green vegetables, giblets</td>
<td>Stimulation of cell formation</td>
</tr>
<tr>
<td>Biotin</td>
<td>Eggs, fish, giblet</td>
<td>Optimization of cell functions</td>
</tr>
<tr>
<td>Vitamin K₁</td>
<td>Green vegetables (curly kale, broccoli)</td>
<td>Essential factor in the blood clotting system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supports the bone metabolism</td>
</tr>
<tr>
<td>Vitamin D₃</td>
<td>Fish, milk</td>
<td>Supports the bone metabolism</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Fruit, vegetables (esp. paprika, broccoli)</td>
<td>Antioxidant, supports the immune system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Involved in the regeneration of vitamin E</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Required for the collagen synthesis</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Liver, carrots, tuna, cheese</td>
<td>Supports cell division and function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Important for the immune system</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Vegetable and fish oils, nuts, eggs, giblets</td>
<td>Antioxidant, supports the immune system</td>
</tr>
</tbody>
</table>

Antioxidant effects
Supports the immune system
Important for the blood formation and oxygen transport in the blood
Important effect on thyroid function
Components of antioxidant enzymes
Support the immune system


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