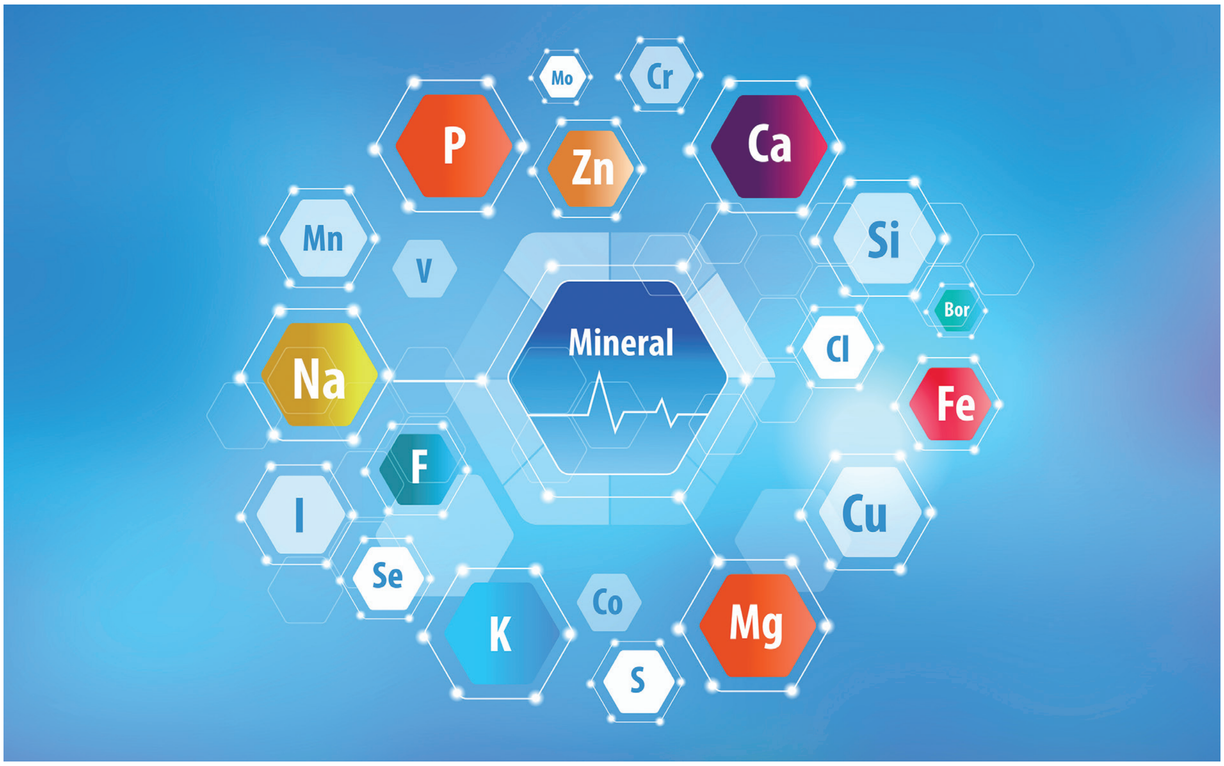

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Micronutrients for the immune system: vitamin A, vitamin D, magnesium and zinc

Philipp Gebhardt

The immune system protects us from pathogens such as bacteria, viruses and fungi. Various micronutrients are of particular importance for the functioning of our body's defences. Vitamin A, zinc, vitamin D and magnesium are essential for the normal function of the immune system. However, there is often insufficient intake with food, so that supplementation can be useful.

Vitamin A

Vitamin A is the name of a group of fat-soluble vitamins that are contained in animal foods as retinols. Plant sources contain provitamin A as beta-carotene, that can be converted into vitamin A in the body.(1) Vitamin A is essential for our health as it is involved in regulating the growth and specialization (differentiation) of practically all cell types. Adequate intake is a prerequisite for various physiological processes such as vision, embryonic development and the normal function of the immune system. In developing countries, vitamin A deficiency is a major health problem that affects around a third of children. An inadequate supply of vitamin A can have a significantly negative impact on the course of various infectious diseases such as measles, tuberculosis and malaria. Vitamin A deficiency is one of the leading causes of preventable cases of blindness worldwide, especially in children and women of childbearing age. A deficiency in the vitamin predisposes to various skin diseases and contributes to growth disturbances, which affect around 160 million children worldwide.(2)

The German Nutrition Society recommends a daily intake of 850 µg so-called retinol activity equivalents for adult men and correspondingly 700 µg for adult women. It is assumed that 1 µg retinol can be formed in the body from 12 µg beta-carotene, so that a daily intake of 10.2 or 8.4 mg beta-carotene would be required in a purely plant-based diet. However, genetic polymorphisms affecting the enzyme beta-carotene monoxygenase, which converts beta-carotene into vitamin A, are widespread and affect the organism's ability to convert provitamin A into vitamin A.(1) Around one in five Europeans does not get enough vitamin A through the diet. Children in particular are often affected by an undersupply, as they have a comparatively high need, but at the same time have a low storage capacity. People with fat absorption disorders, such as exocrine pancreatic insufficiency, as well as diabetics and people with hyperthyroidism are also considered to be risk groups, as they cannot absorb fat-soluble nutrients well or can only convert vegetable carotenoids into vitamin A to a limited extent. As a symptom of a vitamin A deficiency, those affected often experience night blindness, an impairment of vision in dim light. Without sufficient Vitamin A, the rod cells of the eye cannot produce enough rhodopsin, which is formed from the vitamin A derivative 11-cis-retinal and the protein opsin. (Fig. 1).

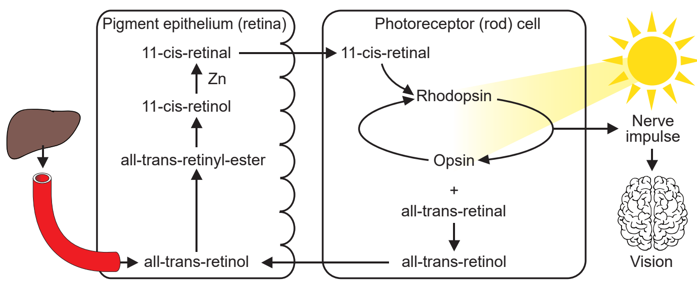

Fig. 1: Vitamin A is stored in the liver and the pigment epithelial cells of the retina in the form of retinyl esters. As all-trans retinol, the vitamin can be bound to so-called retinol-binding proteins and transported in the blood. If necessary, retinyl esters are hydrolyzed to 11-cis retinol and, depending on zinc, oxidized to retinal. In the rod cells of the retina, retinal is bound to the protein opsin to form the light-sensitive receptor molecule rhodopsin. The photons of the light catalyze the isomerization of the cis-retinal to trans-retinal, which separates from the rhodopsin and triggers the creation of a nerve impulse that is processed by the visual cortex in the cerebral cortex. Since the rod cells are primarily responsible for seeing in low light conditions, vitamin A deficiency is associated with the symptom of night blindness.

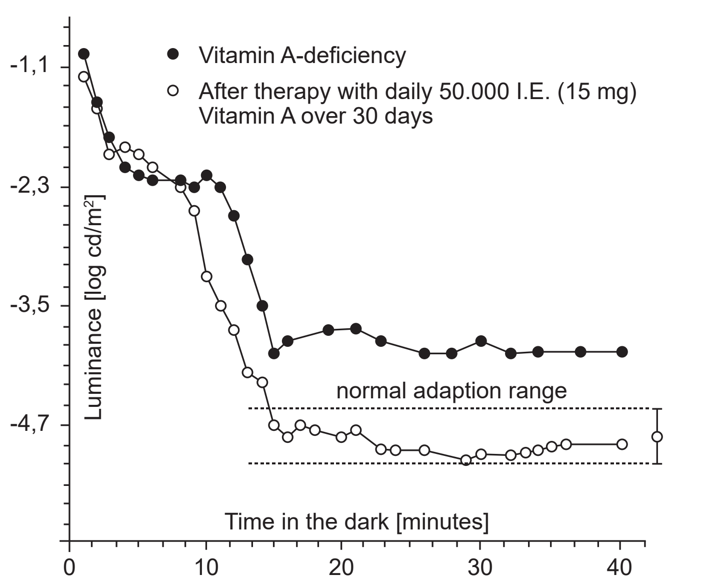

Fig. 2: In contrast to phototopic vision, in which colours can be perceived with sufficient brightness, with so-called scoptic vision with the rods in low light conditions, no color perception is possible. Rod vision depends on the rhodopsin concentration in the rod cells. Since rhodopsin first has to be formed in the rod cells, dark adaptation takes a certain amount of time. In the case of vitamin A deficiency, rhodopsin formation is disturbed, so that vision is not possible at low luminance levels and night blindness occurs. The supplementation of 15 mg vitamin A daily for 30 days can restore normal dark adaptation. (4)

It is assumed that a regular daily intake of 3 mg vitamin A (3,000 µg retinol activity equivalents) is harmless for adults (so-called tolerable upper intake level). (3) To compensate for an existing vitamin A deficiency, it can make sense to supplement higher doses over a short period of time, e.g. 15 mg of vitamin A daily for 30 days (Fig. 2).

Zinc is an essential trace element for the metabolism of vitamin A. The enzyme retinol dehydrogenase, which converts 11-cis-retinol to 11-cis-retinal, as well as the enzyme beta-carotene monooxygenase, which converts beta-carotene into two molecules of retinal, depend on adequate zinc concentrations for their function.

Zinc

An adult's body contains around 1.5 to 3 g of zinc, with more than 95 % of the trace element being found in the cells of the muscles (around 57 %), the bones (around 29 %) and other tissues. Only about 0.1 % of the cation is dissolved in the blood plasma or bound to albumin, with typical concentrations in the range of 1 µg/ml blood. Zinc forms a cofactor or is part of more than 300 enzymes and an even larger number of other proteins, such as transcription factors, which control the conversion of DNA into RNA. An inadequate zinc supply is associated with growth disorders, anaemia, disorders of the hormonal balance, poor wound healing and impaired vision. A zinc deficiency is also associated with a deterioration in the immune response to pathogens and an increase in the unspecific activation of T cells. As a cofactor of the enzyme superoxide dismutase, zinc plays a decisive role in the neutralization of reactive superoxide radicals, which are produced in the metabolism during reactions with oxygen (oxidative stress).

According to data from the National Consumption Survey II, 21 % of women and 32 % of men in Germany do not achieve the recommended amounts of zinc through the diet.

Phytic acid, which is mainly contained in pulses, cereals and oilseeds, is used by the plants as a store for cations such as iron and zinc. As

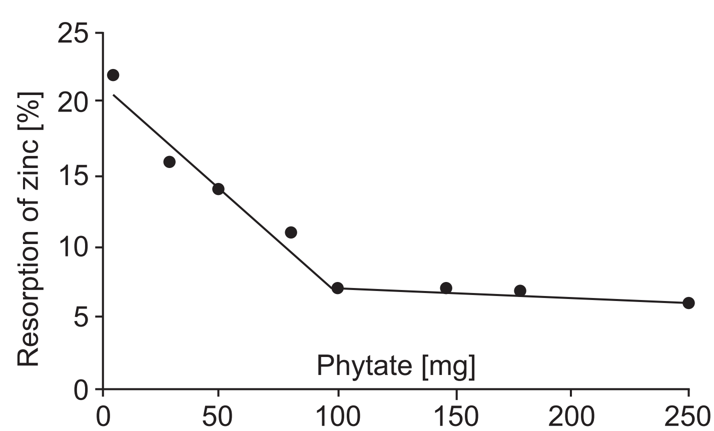

Fig. 3: Phytic acid contained in plant-based foods forms insoluble complexes with zinc and inhibits the uptake of the trace element in the small intestine. The phytate content of a meal correlates inversely with the absorption of the contained zinc. (5)

a complexing agent, it can insoluble bind the zinc contained in the food and thereby hinder its absorption in the small intestine (Fig. 3).

Depending on the phytate intake, the German Nutrition Society recommends a daily zinc intake of between 7 and 10 mg for women and between 11 and 16 mg for men. It is believed that zinc needs increase with age. In an investigation with study participants between the ages of 65 and 82 years, the daily supplementation of 10 mg zinc for seven weeks had a significantly positive effect on the immune system. An improved control of the immune response could be shown, which was expressed in a reduction of proinflammatory metabolic parameters with simultaneously improved immune defense. According to this, dietary supplementation with zinc does not lead to a general inhibition of the immune response compared to certain anti-inflammatory pharmacotherapies. Zinc improves the immune response to pathogens and reduces the incidence of infections. (6)

Vitamin D

Vitamin D plays important roles in maintaining calcium levels in the blood and in building and maintaining our bones. In addition, it is of central importance for the regulation of the immune response by T helper cells. Vitamin D reduces the formation of Th1 helper cells, which are held responsible for excessive immune reactions, such as those that occur in autoimmune diseases. (7) Vitamin D promotes the formation of Th2 helper cells and regulatory T cells, which suppress excessive activation of the immune system and enable adequate self-tolerance. An undersupply of vitamin D goes hand in hand with a significantly increased risk of bone diseases, infections and many other diseases. Vitamin D is formed in the skin by radiation from the sun. Contrary to an often published opinion, however, in the latitudes of Germany, vitamin D formation through UV exposure of the skin is not possible from October to March, since the solar radiation hits the earth's surface too flat and the relevant UV-B portion of the radiation is absorbed by the atmosphere. (8) Vitamin D is found in certain foods. The amounts ingested are usually too small to influence the vitamin D level to a relevant extent. Due to our modern way of life, in which we are usually not sufficiently exposed to the sun, inadequate supply is widespread also in the summer months. It is assumed that around 40 % of the European population are affected by a deficient vitamin D supply (< 30 ng/ml 25(OH)vitamin D3) or that around 13 % have a severe deficiency (<12 ng/ml 25(OH)vitamin D3). (9)

The vitamin D requirement can be covered safely by supplementing the diet with vitamin D3. The quantities required for this can easily be calculated by multiplying the target value in ng/ml 25(OH)vitamin D3 by the body weight. To achieve a value of 30 ng/ml, a 70 kg adult without additional sun exposure would have to supplement around 2,100 IU of vitamin D3 (52.5 µg cholecalciferol) per day (30 ng/ml x 70 kg). Vitamin D3 has a favourable therapeutic ratio. A daily intake of up to 4,000 IU (100 µg) is considered to be safe by the European Food Safety Authority (EFSA).

Vitamin D develops its effect by binding to the vitamin D receptor in the cell nucleus ("vitamin D hormone"). The retinoid receptor forms a partner receptor, which is assumed that its activation by vitamin A improves the DNA binding of the vitamin D receptor and increases the transcription of the target RNA (Fig. 4).

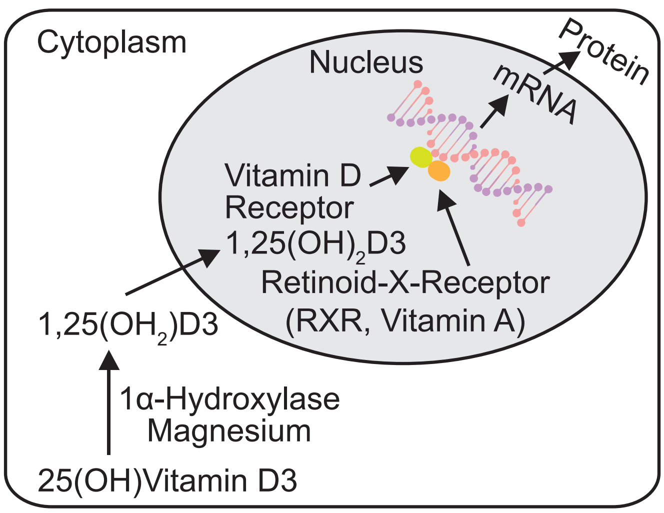

Fig. 4: The storage form 25(OH)vitamin D3 is converted into 1,25(OH)2-vitamin D3 depending on magnesium. The active vitamin D metabolite binds to the vitamin D receptor in the cell nucleus. The retinoid receptor forms a partner that improves DNA binding and supports the transcription of the DNA.

Sufficient magnesium concentrations are necessary for the vitamin D metabolism. The hydroxylases, which convert the prohormone cholecalciferol into the storage form 25(OH)vitamin D3 and convert the storage form into the active form 1,25(OH)2-vitamin D3, require magnesium as a cofactor.

Magnesium

An adult's body contains around 24 g of magnesium. About 40 % of the magnesium in the blood plasma is bound to proteins; the normal serum level is 1.8-2.6 mg/dl. Most of the magnesium is found in our bones, which can store it and release it when it is less absorbed. A normal magnesium blood level therefore does not rule out magnesium deficiency. An inadequate supply of magnesium predisposes to osteoporosis and broken bones. Magnesium is involved in more than 600 enzyme reactions as an enzyme component or coenzyme. Free magnesium ions influence the potential on cell membranes and act as second messengers in the immune system. They stabilize the resting potential of excitable muscle and nerve cells and the cells of the autonomic nervous system. Magnesium is also an essential cofactor of the enzyme ATP synthase, which in the mitochondria, the "power plants of our cells", regenerates adenosine diphosphate (ADP) to adenosine triphosphate (ATP), which is the universal energy carrier of our metabolism. As a magnesium-ATP complex, magnesium is involved in almost all energy-intensive processes.

It could be shown that a magnesium deficiency is associated with an increased formation of proinflammatory tissue hormones. On the other hand, magnesium supplementation appears to have a positive effect on the formation of certain cytokines and prostaglandins. In inflammatory diseases of the respiratory tract, magnesium promotes the relaxation of the smooth bronchial muscles, so that supplementation can also contribute to bronchodilation in addition to its anti-inflammatory effect. (10)

The German Nutrition Society recommends a daily intake of 300 mg magnesium for adult women and 350 mg for adult men. According to data from the National Consumption Survey II, around 29 % of women and 26 % of men in Germany do not reach these intake levels. Other studies show an average daily magnesium intake of only around 200 mg in women and 250 mg in men. (11) There is a particular risk of magnesium deficiency in diabetics, who excrete more glucose via the kidneys when their blood sugar levels are too high. Important minerals such as magnesium are also lost with the urine.

Vitamin A, vitamin D, magnesium and zinc are involved in various immune functions in the metabolism. With regard to their mechanism of action, the micronutrients are interdependent or support each other in their effect. Since deficiency is widespread, care should be taken to ensure adequate supply. In view

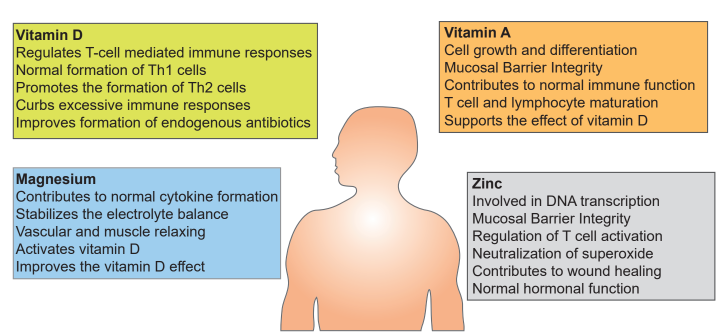

Fig. 5: Vitamin A, vitamin D, magnesium and zinc contribute to the normal function of the immune system. The micronutrients support each other in their effect.

of the current coronavirus pandemic, there are many rational arguments for supplementation. Inadequate intake can adversely affect the course of the disease. On the other hand, supplementation can help to make the course of the disease milder.

Dietary supplements also seem to improve the effectiveness of vaccination. As part of the investigation of an influenza vaccination with 79 children, it was found that supplementation with vitamins A and D can improve the vaccination response, especially if there was a deficit beforehand. (12) Due to the fact that there are no side effects, the addition of appropriate micronutrients is also particularly recommended in the context of vaccination.

References

(1) Lietz, G., Oxley, A., Leung, W., & Hesketh, J. (2012). Single nucleotide polymorphisms upstream from the β-carotene 15, 15'-monoxygenase gene influence provitamin A conversion efficiency in female volunteers. The Journal of nutrition, 142(1), 161S-165S.

(2) Borel, P., & Desmarchelier, C. (2017). Genetic variations associated with vitamin A status and vitamin A bioavailability. Nutrients, 9(3), 246.

(3) Scientific Committee on Food. (2006). Tolerable upper intake levels for vitamins and minerals. European Food Safety Authority.

(4) Russell, R. M. (2000). The vitamin A spectrum: from deficiency to toxicity. The American journal of clinical nutrition, 71(4), 878-884.

(5) Lönnerdal, B. (2002). Phytic acid–trace element (Zn, Cu, Mn) interactions. International Journal of Food Science & Technology, 37(7), 749-758.

(6) Kahmann, L., Uciechowski, P., Warmuth, S., Plümäkers, B., Gressner, A. M., Malavolta, M., ... & Rink, L. (2008). Zinc supplementation in the elderly reduces spontaneous inflammatory cytokine release and restores T cell functions. Rejuvenation research, 11(1), 227-237.

(7) Komisarenko, Y. I., & Bobryk, M. I. (2018). Vitamin D deficiency and immune disorders in combined endocrine pathology. Frontiers in endocrinology, 9, 600.

(8) Webb, A. R., Kline, L., & Holick, M. F. (1988). Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. The journal of clinical endocrinology & metabolism, 67(2), 373-378.

(9) Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Köstenberger, M., Berisha, A. T., ... & Malle, O. (2020). Vitamin D deficiency 2.0: an update on the current status worldwide. European journal of clinical nutrition, 74(11), 1498-1513.

(10) Tang, C. F., Ding, H., Jiao, R. Q., Wu, X. X., & Kong, L. D. (2020). Possibility of magnesium supplementation for supportive treatment in patients with COVID-19. European Journal of Pharmacology, 173546.

(11) Vormann, J., & Anke, M. (2002). Dietary magnesium: supply, requirements and recommendations-results from duplicate and balance studies in man. Journal of Clinical and Basic Cardiology, 5(1), 49-53.

(12) Patel, N., Penkert, R. R., Jones, B. G., Sealy, R. E., Surman, S. L., Sun, Y., ... & Hurwitz, J. L. (2019). Baseline serum vitamin A and D levels determine benefit of oral vitamin A&D supplements to humoral immune responses following pediatric influenza vaccination. Viruses, 11(10), 907.

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