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Literature Report
Summaries
of recent studies

Nutritional effects of micronutrients
(vitamins, trace elements, phytonutrients)
on the immune system

Preface

The immune system is one of the most complex and most cross-linked organ systems of our body. Its main functions include protection against infections, tumor surveillance and an active role in tissue regeneration.

It is a complex system which, for the maintenance of its functions, requires a sufficient supply of micronutrients, such as vitamins, trace elements, phytonutrients and antioxidants.

Usually nutrition warrants the basic supply needed by the immune system, among others through micronutrients. These are capable of influencing the immune response, e.g. through the provision of an adequate quantity of antioxidative systems for the resistance to and protection against free radicals.

If the immune system is exposed to particularly stressful conditions, such as acute or chronic infections, micronutrient requirements will increase. Often normal diet cannot cover these requirements any more. In order to ensure an adequate supply, the deficient substances can be supplemented by a micronutrient combination specifically protecting the immune system.

Nutritionists emphasize the importance of micronutrients to the immune system.

Micronutrients (vitamins, trace elements, phytonutrients) play a major role for an intact immune system. It is well known that an increased intake of vitamins C, E, phytonutrients (carotenoids, bioflavonoids), zinc and selenium as natural antioxidants will support the immune cell function.

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(COPD)

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Effects of a multivitamin supplementation on the antioxidant defense system of healthy humans

Effects of multinutrient supplementation on antioxidant defense systems in healthy human beings
Cheng T, Zhu Z, Masuda S, Morcos NC, et al. J Nutr Biochem 2001;12(7):388–95.

Study design, patients and methods

In this double-blind, placebo-controlled trial, 34 healthy subjects (21 males and 13 females of an average age of 24.6 years) were assessed to find out whether multivitamin supplementation would improve their antioxidant protection.

The study participants were divided into two groups, one received a multivitamin and mineral product, the other was given a placebo. Blood samples were taken two weeks before starting supplementation, on the first day of multivitamin supplementation, and 5 and 16 weeks after starting supplementation.

The following parameters were measured:

- blood levels of vitamins C and E, beta-carotene and selenium,
- erythrocyte vitamin E levels,
- catalase, glutathione peroxidase and superoxide dismutase activities,
- total glutathione, oxidized and reduced glutathione,
- erythrocyte susceptibility to oxidative damage after incubation with free radicals.

Results

After 5 weeks of supplementation, plasma levels of vitamins C, E and beta-carotene had significantly increased. After 16 weeks, catalase and glutathione peroxidase activity was significantly higher, but not superoxide dismutase activity. Moreover, the quantity of reduced glutathione had risen. After 5 weeks, the erythrocytes in the group of subjects having received multinutrient supplementation were more resistant against oxidative stress.

Conclusion

The short-term supplementation of vitamins and minerals for 16 weeks can actually improve the antioxidant status and the activity of antioxidant enzymes. The resistance of red blood cells to peroxidation processes could also be significantly enhanced.



Carotenoid levels of lung macrophages can be influenced

Plasma and lung macrophage responsiveness to carotenoid supplementation and ozone exposure in humans
Steck-Scott S, Arab L, Craft NE, et al. Eur J Clin Nutr 2004;58:1571–9.

Study design, patients and methods

In this study, investigators wanted to find out how carotenoid levels in plasma and lung macrophages can be changed by vegetable juice supplementation or ozone exposure. For 14 days 23 healthy volunteers were given a diet which was lacking in fruit and vegetables and a supplementation with carotenoids (26.05 mg daily, vegetable juice), vitamins C and E (capsule 250 mg and 33.5 mg daily, respectively), or placebo. In addition to blood analyses, the carotenoid content in lung macrophages, collected through bronchoalveolar lavage, was determined after a two-hour intermittent physical exercise test under ozone exposure (0.4 ppm or 784 $\mu\text{g}/\text{m}^3$). An exercise test in filtered air at the beginning of the study served as control (sham exposure).

Results

In the vegetable supplementation group plasma levels of almost all carotenoids contained in the vegetable juice increased significantly. The content of alpha-carotene and trans- and cis-lycopene in lung macrophages also increased. While ozone exposure in the placebo group resulted in a significant fall in plasma carotenoids in some cases, corresponding levels remained largely unchanged in the supplementation group, even under ozone exposure.

Conclusion

The high ozone (O_3) load of the air is a global problem. Among other factors, ozone, through lipid peroxidation, leads to the formation of free radicals that can attack the lung tissue and result in a significant reduction of plasma carotenoids. Within a relatively short period of time, supplementation of carotenoids will raise plasma and lung macrophage carotenoid concentrations and counteract the fall in plasma levels under ozone exposure.



Influence of micronutrient supplements on immune response and infectious diseases in 50–65 year old individuals

Influence of micronutrient supplement on immune responses and infection-related illnesses in 50-65 year old individuals
Chandra RK. Nutr Res 2002;22:5–11.

Study design, patients and methods

Placebo-controlled trial including 44 healthy subjects (22 men and 22 women) between 50 and 65 years of age, of whom 19 (43.2%) showed a suboptimum supply of one or more micronutrients at the beginning of the study. Over a 12-month period, subjects took a daily combination of vitamins A, B₁, B₂, B₆, B₁₂, niacin, folic acid, vitamins C, D, E, beta-carotene as well as minerals and trace elements (calcium, magnesium, iron, zinc, copper, selenium, iodine), or a placebo. After 3 months study participants underwent an influenza vaccination, and 12 weeks after that the antibody level was assessed. Every second week the study participants were interviewed in order to investigate their health status (fever, cough, etc.).

Furthermore, for the assessment of their infection status, the concentrations of C-reactive protein and the erythrocyte sedimentation rate were measured, X-ray images of sinuses and chest were made and blood, sputum and urine cultures were taken and analyzed. At baseline and after 6 and 12 months nutrient concentrations and defined immune responses were measured in the blood of the subjects.

Results

After a 6-month supplementation only one subject still had an iron deficiency which normalized after 12-month supplementation. In the control group there was no change in the frequency of nutrient deficiencies. The micronutrient group demonstrated a significantly higher antibody response after influenza vaccination and a significantly greater increase in T lymphocytes and CD4+ helper T cells. In the group with micronutrient supplementation higher interleukin-2 values were found. In this group the individuals who had shown one or more nutrient deficiencies initially benefited most. During the observation period (1 year) the supplementation group had 11.1 ± 0.8 days and the placebo group 23.7 ± 2.1 days of infection-related illness ($p < 0.01$). The beneficial effect on morbidity was greatest during the last 6 months of supplementation.

Conclusion

In the group of 50- to 65-year-old individuals the dietary supplementation of a micronutrient combination resulted in a significantly stronger antibody response after influenza vaccination and a lower incidence of infection.



Effect of a multivitamin and mineral supplementation on quality of life and infection

Effect of a multivitamin and mineral supplement on infection and quality of life.

A randomized, double-blind, placebo-controlled trial

Barringer TA, Kirk JK, Santaniello AC, Foley KL, Michielutte R, et al. Ann Intern Med 2003 4;138(5):365–71.

Study design, patients and methods

The randomized, placebo-controlled, 12-month double-blind study was conducted at two academic primary care clinics including 130 subjects. Study participants were randomly assigned to two groups of comparable age structure (at least 45 years) and comparable type-2 diabetes prevalence.

Half of the subjects (n=63) received a multivitamin and mineral supplement daily for one year, while the other half (n=67) received a placebo. The primary endpoint of the study was the incidence of infection. In addition, the study participants recorded daily any symptoms from which the attendant doctors might diagnose infectious diseases according to standard criteria, such as respiratory tract infections, influenza-like syndrome and gastrointestinal and urinary tract infections. The secondary endpoint of the study was the change in quality of life.

Results

Two thirds of the study subjects were obese, and approximately 30% had type-2 diabetes. About 18% demonstrated a micronutrient deficiency (defined as intake below the 33rd percentile of the recommended daily allowance for zinc, selenium, iron, folic acid and vitamins A, C, E and B₆).

Among the type-2 diabetics the proportion of subjects with subclinical micronutrient deficiencies was particularly high. After 12 months, one or more infections could be diagnosed in 73% of the subjects in the placebo group, whereas in the micronutrient supplement group only 43% of patients had infections. This corresponds to a significant 41% reduction in infection risk. Compared with the placebo group, the number of days of absenteeism (defined as days during which planned activities could not be performed) could be significantly reduced with the intake of the supplement, i.e. from 57% to as low as 21%. The greatest benefit from the micronutrient supplementation was experienced by type-2 diabetics. Thus, 93% of the placebo, but only 17% of the micronutrient group reported infections. Days of absenteeism were recorded for 89% of the placebo and for no diabetic from the treatment group.

Conclusion

The long-term supplemental supply with a micronutrient combination significantly decreased the general infection risk by 41%. Even more pronounced was the benefit for type-2 diabetics, whose infection risk could be reduced by 82%.



Vitamin E supplementation strengthens the immune system of elderly people

Vitamin E and immune response in the aged: molecular mechanisms and clinical implications

Meydani SN, Han SN, Wu D, et al. *Immunol Rev* 2005;205:269–84.

Study design, patients and methods

In this review article, Meydani and colleagues summarize their own studies and the work of other researchers who have worked on the nutritional effects of vitamin E on various immune functions. Besides the possible cellular mechanisms, the clinical impact of vitamin E intake was in the center of interest. In many people the efficacy of the immune response decreases with increasing age. This fact is also influenced by the nutritional status, and vitamin E plays an especially important role in this context.

The highly potent antioxidant protects immune cells against oxidative damage and thus ensures their normal function. However, many elderly people in particular do not take enough vitamin E with their diet.

Results

Numerous studies confirm the positive effect of a vitamin E supplementation on the immune function of the elderly. Thus, two trials showed an association between the level of plasma vitamin E and the development of a delayed-type hypersensitivity response (type-IV response) in the skin or the response to a hepatitis-B vaccination.

Moreover, various clinical trials and animal models suggest that by the supplemental administration of vitamin E the resistance in old age, especially against viral infections of the upper airways including influenza, may be improved. Obviously there are two mechanisms that are responsible for the immune regulating effects of vitamin E.

On the one hand, vitamin E acts indirectly as it reduces the formation of immune suppressant factors, such as PGE₂, and on the other hand vitamin E supports the cell division capacity and interleukin-2 production of naive T cells.

Conclusion

For an undisturbed functioning of immune cells adequate levels of vitamin E with its antioxidant action are needed. Numerous scientific studies confirm that the vitamin E supplementation in elderly people improves immune response and thus possibly prevents infections. Therefore vitamin E supplementation of the normal diet could be a practical and cost-efficient approach leading to the reduction of infection incidence in this age group.



Influence of vitamins and trace elements on the incidence of respiratory infection in the elderly

Influence of vitamins and trace elements on the incidence of respiratory infection in the elderly
Jain AL. Nutr Res 2002;22:85–87.

Study design, patients and methods

Randomized and placebo-controlled trial with 36 healthy subjects between 51 and 78 years of age (11 men and 7 women in each group). Over a period of 12 months a micronutrient combination including vitamins (vitamin A, C, D, E, B₁, B₂, B₆, B₁₂, niacin, folic acid, beta-carotene), trace elements and minerals (calcium, magnesium, iron, zinc, copper, selenium, iodine), or placebo (containing calcium and magnesium) was administered every day.

At the end of each month, study participants were asked to get in contact with the investigators to report any symptoms or discomfort. Additionally, the subjects were medically examined, and in order to assess the infection status, the erythrocyte sedimentation rate and white blood cell count were measured, X-ray images of the frontal sinus and the chest were made and sputum cultures incubated.

Results

In the supplemented individuals fewer episodes of respiratory infection were observed. However, this effect was statistically not significant. The micronutrient group experienced also significantly fewer days of illness because of airway infections (14 ± 2 days) than the placebo group (29 ± 4 days, $p < 0.03$). Compared with the placebo group, the supplement group took smaller amounts of antibiotics during the observation period (supplement group 27 ± 4 days vs. placebo group 58 ± 5 days, $p < 0.02$).

Conclusion

The supplementation of vitamins and trace elements significantly reduced the number of days of illness because of airway infections. The investigators recommended therefore the regular supplementation for people aged 50 years or older in order to reduce costs, e.g. costs due to the much more expensive antibiotics for the treatment of infections compared with lower costs of the multinutrient supplement.



Nutritional formula enhances immune function and reduces upper respiratory tract infections in seniors

Nutritional formula enhanced immune function and reduced days of symptoms of upper respiratory tract infection in seniors
Langkamp-Henken B, Bender BS, Gardner EM, et al. J Am Geriatr Soc 2004;52(1):3–12.

Study design, patients and methods

In this prospective, randomized, placebo-controlled, double-blind trial, seniors (>65 years of age) were administered a combination of micronutrients (vitamins and trace elements) or placebo over a period of 183 days (micronutrient group: 7 men and 9 women, control group: 6 men and 12 women). The study participants recorded any symptoms of upper respiratory tract infection every day. Also, on days 57 and 183, the antibody response and lymphocyte proliferation after influenza vaccination were assessed.

Results

Eighteen individuals in the control group and 16 subjects in the experimental group completed the study. The subjects who had taken micronutrients showed 50% fewer days of illness compared with the control group ($p=0.08$). For the control group, a median of 3 days of illness (airway symptoms on 0–69 days, in total 156 days) was measured, while the median in the verum group was 0 days (range 0–49, in total 78 days).

On day 57, 41% of the control group and 87% of the supplemented group achieved a 4-fold or greater increase in serum antibody titer to influenza type A/Beijing. Also the lymphocyte proliferation after influenza vaccination was greater in the treatment group than in the control group (median 1,365 cpm*, range 0–14,955 cpm, vs. 136 cpm, range 0–4,270 cpm).

Conclusion

Older people consuming a micronutrient combination experienced a substantially enhanced immune function and suffered for a shorter time from symptoms of upper respiratory tract infections. In addition, antibody response after influenza vaccination was considerably stimulated.

* cpm: counts per minute



Effect of multivitamin supplements on HIV disease progression and mortality

A randomized trial of multivitamin supplements and HIV disease progression and mortality
Fawzi WW, Msamanga GI, Spiegelman D, et al. *N Engl J Med* 2004;351(1):23–32.

Study design, patients and methods

In this double-blind, randomized, placebo-controlled trial scientists examined in 1,078 HIV-infected, pregnant women from Tanzania the effect of micronutrient supplements on the progression of clinical disease and the risk of HIV-related complications. Besides this, the CD4+ cell count and viral load were determined. The women were enrolled in the study over a two-year period starting in April 1995.

Various combinations of vitamins were tested. The first group received vitamin A and beta-carotene only, the second group received a multivitamin product containing B vitamins and vitamins C and E, the third group received the multivitamin product plus vitamin A and beta-carotene. A placebo group served as controls. Till the end of the study in August 2003, the patients were followed up and the results were evaluated.

Results

Of 271 women who had received the multivitamin product, 67 had progressed to disease stage 4 (according to WHO definitions) or died. Among 267 women who had taken the placebo, this was true for 83 women (24.7% vs. 31.1%, relative risk 0.71). The multivitamin product reduced the risk of HIV-related signs of disease considerably. These clinical signs included thrush, oral ulcers, difficult swallowing, nausea and vomiting, fatigue and skin rash.

Furthermore, the multivitamin product resulted in significantly higher CD4+ and CD8+ cell counts. Due to the significant viral load reduction by 0.18 Log₁₀ steps, the time to progression to AIDS or death was increased by approx. 30%.

Conclusion

The authors showed that the dietary effect of multivitamins may delay progression of HIV infection and increase the time to initiation of antiretroviral therapy – accompanied by the corresponding cost reduction. Additionally, the risk of HIV-related complications can be reduced.



Orthomol® Immun enhances the immune system and reduces the number of sick days

Effects of nutritional supplements on health
Hofmeister M. Ernähr Med 2005;20(3):115–22.

Study design, patients and methods

For an interventional study, 54 workers employed in the service/retail sector were divided into two groups. The intervention group received Orthomol® Immun powder every day during four winter months (2002/12 to 2003/03), the control group did not receive any supplemental micronutrients. Both groups matched each other in age and gender and did the same kind of work; they were medically examined, and a standardized interview was conducted both at baseline and after completion of the study. On this basis various health-related, immunological and quality of life parameters were assessed.

Results

The general health status and the defensive strength of the immune system were improved in the intervention group who had received Orthomol® Immun: After a 4-month intake of micronutrients vitality was increased by 39.5%, quality of life by 29.6% and the general health status by 31.7%. Blood chemistry showed a significant proliferation of immunoactive cells (monocytes +15.3%, T lymphocytes +5.3%, T helper cells +6.9%, natural killer cells +21.6%). The immune status had also significantly improved (activated T cells: -70.9%, IgM: -7.6%, C-reactive protein: -59.6%, IgA: +6.9%, IgG: +6.7%). With the micronutrient combination the number of sick days could be reduced to a highly significant degree, i.e. by 75.6% compared with the sick days in the previous winter season ($p < 0.001$). In the control group the number of sick days even increased.

Conclusion

The regular intake of Orthomol® Immun, a dietary food for special medical purposes, during the winter months which usually put a greater burden on health, leads to an improvement in health status, quality of life and specific immune parameters. As a result of these effects, sick days were reduced by 75.6% compared with the figures in the previous winter season. The calculation of direct and indirect costs as “return on investment in human health” showed a positive cost-benefit ratio of 1:1.9.



Low levels of antioxidants in patients with severe bronchial asthma

Plasma concentrations of dietary and nondietary antioxidants are low in severe asthma

Misso NLA, Brooks-Wildhaber J, Ray S, et al. Eur Respir J 2005;26:257–64.

Study design, patients and methods

The objective of this cross-sectional study was to determine in how far the plasma levels of various dietary (carotenoids, vitamins C and E) or endogenous (bilirubin, albumin, uric acid) antioxidants differed between asthma patients and healthy subjects. Fifty-three individuals with mild to moderate asthma, 28 with severe asthma and 43 healthy controls were asked to complete a food frequency questionnaire to provide information about their eating habits. All were medically examined.

Results

Compared to the female subjects, males took less vitamin C and alpha- and beta-carotene, especially those suffering from severe asthma. In all subjects the intake of vitamin C and carotenoids with the diet correlated with the plasma levels of vitamin C and alpha- and beta-carotene. In comparison to the patients with milder forms of asthma and the control group, those suffering from severe asthma had significantly lower vitamin C levels. Moreover, the plasma vitamin E concentrations (adjusted for cholesterol levels) of both patient groups were significantly lower than those of the healthy controls. Patients suffering from severe asthma had significantly lower plasma levels of the endogenous antioxidants bilirubin and albumin, as compared to the other two groups. Using a multivariate regression analysis, low vitamin C and bilirubin plasma levels, high total cholesterol and a low socioeconomic status were independently correlated with severe asthma. The blood albumin concentrations were positively and the cholesterol levels negatively correlated with pulmonary function. Intake of dietary supplements significantly improved the expiratory capacity of the lung (FEV1*).

Conclusion

Chronic inflammation of the respiratory tract in asthmatic patients leads, among other things, to the formation of reactive oxygen compounds, and thus to increased oxidative stress. Low plasma levels of specific antioxidants are associated with a severe course of the disease in asthmatic patients. This could lead to an oxidative imbalance and accelerate the progression of the disease.

A higher intake of antioxidants with the diet or as dietary supplements may help to reduce the degree of severity of bronchial asthma.

* FEV1: Expiratory flow per second, Forced Expiratory Volume



Patients with mild asthma show an altered pulmonary antioxidant status

Altered lung antioxidant status in patients with mild asthma

Kelly FJ, Mudway I, Blomberg A, et al. *Lancet* 1999;354(9177):482–3.

Study design, patients and methods

Twenty patients with mild asthma (10 men, 10 women, 104% FEV₁, average age 29.1 years) and 20 healthy controls (10 men, 10 women, 101% FEV₁, average age 25.5 years) participated in this study. All subjects were non-smokers, and none of them took any dietary antioxidant supplementary or antiinflammatory drugs. Asthmatic patients only used beta₂ agonists for asthma control. The antioxidant concentration was determined in nasal lavage fluid, bronchial wash and in bronchoalveolar lavage fluid (BAL).

Results

The asthma patients had divergent levels of vitamin C, vitamin E and urate (uric acid salt) in nasal lavage fluid, bronchial wash and in BAL, whereas the glutathione concentrations were comparable with those of the controls. The vitamin C levels in the bronchial wash of the asthma patients were particularly low or non-detectable, although the plasma vitamin C levels were comparable to those of the control group. The vitamin E levels in bronchial wash and in BAL of the asthma patients were lower although they had higher plasma vitamin E concentrations than the controls. The urate levels of the asthma patients were lower in both plasma and nasal lavage fractions, but higher in bronchial wash and BAL. This is probably due to a compensation of the low vitamin C and vitamin E levels. Asthma patients showed higher amounts of oxidized glutathione in bronchial wash and BAL.

Conclusion

In the chronically inflamed respiratory tract of asthmatic patients inflammatory cells produce and secrete a larger than normal amount of reactive oxygen species. The local oxidative stress thus depends on the availability of antioxidants in the secretion of the respiratory tract. It was shown that asthma patients have lower vitamin C and vitamin E levels and increased amounts of oxidized glutathione in their airways. This leads to the conclusion that these patients have an increased oxidative stress. The results of the study indicate that insufficient intake of antioxidants may play a role in the development and degree of severity of asthma. Low antioxidant levels could make these patients more susceptible to inhaled irritants and allergens.

* FEV₁: Expiratory capacity per second, Forced Expiratory Volume



Complementary therapy with selenium in asthmatics

Need of complementary therapy with selenium in asthmatics

Gazdik F, Pijak MR, Gazdikova K, et al. *Nutrition*. 2004;20(10):950–2.

Study design, patients and methods

This review article is a summary of several studies reporting on the beneficial influence of selenium supplementation in asthmatics. Oxidative processes caused by free radicals are crucial in the development of inflammatory pathology of bronchial asthma. Selenium as a component of the antioxidant glutathione peroxidase enzyme seems to play a fundamental role in the antioxidant protection system and the immune system of asthmatic patients. The modulation of the antioxidant potential by means of antioxidant supplements is a new and attractive approach to antiasthmatic complementary therapy.

Results

Many studies report a strong association between a reduced glutathione peroxidase activity and/or low serum selenium concentration and the onset of non-allergic and allergic asthma. The selenium glutathione peroxidase activity of patients with non-allergic asthma was significantly lower. Asthma patients had significantly lower plasma and whole-blood selenium levels, and people with lower selenium levels demonstrated a higher asthma risk.

A large representative study found out that the asthma risk is all the higher the less selenium was taken up with the diet (consisting of high-selenium food such as fish or whole-grain cereals). Patients suffering from non-allergic asthma already benefit from a 14-day selenium supplementation. After taking selenium for 96 weeks, the corticoid consumption could also be significantly reduced. Selenium as a component of glutathione peroxidase helps remove harmful organic hydrogen peroxides produced during oxidative metabolism. Thus, selenium prevents damage to the immune cells due to oxidative stress. Selenium also appears to promote cellular immunity. Giving patients selenium will increase the number of cytotoxic lymphocytes, lymphokine activated killer cells and natural killer cells and lead to the up-regulation of the interleukin-2 receptor on T cells and to an enhanced T-cell response.

Conclusion

Asthma patients tend to have increased oxidative activity, lowered selenium status, and decreased activity of glutathione peroxidase. Dietary supplementation with selenium, in combination with the usual asthma medication, will help reduce oxidative stress, enhance the immune response and thus alleviate asthma symptoms.



Increased oxidative stress and altered antioxidant levels in asthmatics

Increased oxidative stress and altered levels of antioxidants in asthma

Nadeem A, Chhabra SK, Masood A, et al. *J Allergy Clin Immunol.* 2003;111(1):72–8.

Study design, patients and methods

Reactive oxygen radicals might play an important role in the pathogenesis of respiratory tract inflammations, such as asthma. In this study, 38 patients with bronchial asthma and 23 control subjects were to be assessed for a potential imbalance between oxidants and antioxidants.

Production of lipid peroxides, superoxide anions, protein carbonyls, protein sulfhydryls, total nitrites and nitrates were determined to serve as a measure for oxidative stress. Superoxide dismutase and catalase activity as well as the blood level of glutathione, glutathione peroxidase activity in the erythrocytes and leukocytes and overall oxidative plasma capacity served as a measure for the antioxidant status.

Results

Asthmatic patients demonstrated a higher superoxide generation from leukocytes and elevated levels of nitrites, nitrates, protein carbonyls and lipid peroxidation products. Their protein sulfhydryl levels, however, were decreased.

Asthmatic patients had higher blood glutathione levels, increased superoxide dismutase activity (in red blood cells) as well as lower glutathione peroxidase activity (in red blood cells and leukocytes). Red blood cell catalase activity and the total antioxidant capacity of plasma were not altered.

Conclusion

Patients with bronchial asthma demonstrated a disturbed balance of oxidants and antioxidants leading to increased oxidative stress. Therefore augmentation of the nutritional antioxidant defences may have a beneficial influence on antiasthmatic treatment.



Carotinoid levels of asthma patients vs. healthy controls

Airway and circulating levels of carotenoids in asthma and healthy controls

Wood LG, Garg ML, Blake RJ, et al. J Am Coll Nutr 2005;24(6):448-55.

Study design, patients and methods

Asthmatic patients often demonstrate elevated oxidative stress and impaired antioxidant protection. Carotenoids are effective antioxidants that may provide protection against asthma by reducing oxidative damage.

For this study the circulating and respiratory tract (sputum) levels of carotenoids of 15 asthmatic patients and 16 healthy controls were determined. Dietary carotenoid intakes were estimated using a questionnaire that had to be filled in every day (so-called 24-hour recall method). Another group of 9 healthy subjects were supplemented with 20 mg/day lycopene, a carotenoid, for a period of 4 weeks to find out whether carotenoid supplementation can improve the antioxidant protection of the respiratory tract.

Results

Despite similar dietary carotenoid intake, the asthmatic patients had significantly lower whole-blood levels of total carotenoids, lycopene, lutein, beta-cryptoxanthin, alpha-carotene and beta-carotene levels in the blood. In the sputum or plasma, however, the carotenoid levels did not differ. In general, the carotenoid levels in the sputum were significantly lower than they were in the blood or plasma. Nevertheless, changes in the plasma carotenoid levels correlated strongly with those in the respiratory tract ($r=0.798$, $p<0.001$). Although a general increase in the carotenoid level in the plasma or sputum could not be detected after lycopene supplementation, a close correlation was observed between the change in carotenoid concentration in the respiratory tract and in plasma ($r=0.908$, $p<0.002$).

Conclusion

Carotenoids may have an important role in asthma pathogenesis. Thus, on the basis of the data derived from this study, a disturbed carotenoid status could be confirmed in asthmatic patients. Asthma patients have lower carotenoid levels in the blood, but not in the plasma or sputum. Increased plasma carotenoid levels as a result of supplementation are also reflected by the carotenoid concentration in the airways.



Balance of leukocyte oxidants and antioxidants in asthma

Leukocyte oxidant and antioxidant status in asthmatic patients

Vural H, Aksoy N, Ceylan E, et al. Arch Med Res 2005;36(5):502–6.

Study design, patients and methods

In bronchial asthma reactive oxygen species are released by activated inflammatory cells, such as leukocytes, in the respiratory tract where they cause an increase in oxidative stress and thus contribute to the inflammatory processes in bronchial asthma. In this study the researchers aimed to determine whether the oxidant-antioxidant balance is changed in leukocytes of patients with bronchial asthma.

For this purpose, blood samples were drawn and leukocytes separated from 38 patients (21 men, 17 women, age 22 to 68 years) and 32 healthy subjects (18 men, 14 women, age 20 to 63 years). Then the following leukocyte parameters were measured:

- activity of the superoxide dismutase (SOD) and glutathione peroxidase (GDH-Px) enzymes,
- malone dialdehyde (MDA) values and thus the lipid peroxidation rate (LPR),
- vitamin C levels.

Results

The leukocytes of the patients with bronchial asthma demonstrated a higher LPR and SOD activity ($p < 0.001$ and $p < 0.05$), whereas GSH-Px activity and vitamin C levels of the patient group were lower ($p < 0.01$ and $p < 0.001$). Thus, the leukocytes of asthmatic patients showed evidence for the presence of oxidative stress which led to an increase in MDA concentration, i.e. lipid peroxidation, and, as a reaction, to increased SOD activity, whereas the vitamin C and GSH-Px levels in the leukocytes of asthmatic patients dropped, as they apparently had inadequate reserves for compensation of the oxidative stress. If the oxidative stress remains at an elevated level, also a decrease in leukocyte SOD activity may be observed in addition.

Conclusion

The results of the study show that patients with bronchial asthma suffer from increased oxidative stress characterized by an imbalance of antioxidants and oxidants. This condition was proved, among other things, by increased lipid peroxidation, i.e. higher MDA level, lower GSH-Px activity, and lower vitamin C level.



Oxidative stress and altered antioxidant concentrations in COPD patients

Antioxidant vitamins (A, C and E) and malondialdehyde levels in acute exacerbation and stable periods of patients with chronic obstructive pulmonary disease

Tug T, Karatas F, Terzi SM. Clin Invest Med 2004;27(3):123–8.

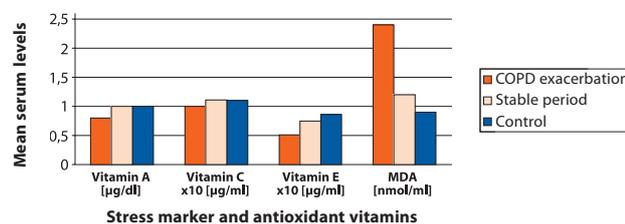
Study design, patients and methods

Prospective study including 24 patients (age 51.8 ± 6.7 years) suffering from chronic obstructive pulmonary disease (COPD), and 23 healthy controls. As oxidative tissue damage seems to be a crucial factor in the pathogenesis of COPD, the aim of the trial was to determine the antioxidant status of COPD patients. The serum concentrations of vitamins A, C and E and the lipid peroxidation product malone dialdehyde were measured before treatment of periods of exacerbation and in stable periods.

Results

Average vitamin A levels during an acute episode amounted to 0.8 ± 0.2 $\mu\text{g}/\text{dl}$ and rose significantly in the stable phase to 1.0 ± 0.2 $\mu\text{g}/\text{dl}$ ($p=0.009$). The average vitamin A level of the controls amounted to 1.0 ± 0.3 $\mu\text{g}/\text{dl}$. No statistic difference was found between the vitamin C levels of COPD patients (acute phase 10.0 ± 2.4 $\mu\text{g}/\text{ml}$ and stable phase 11.1 ± 2.6 $\mu\text{g}/\text{ml}$) and the controls (11.0 ± 2.9 $\mu\text{g}/\text{ml}$).

The vitamin E serum concentration of COPD patients in the acute phase (5.1 ± 2.2 $\mu\text{g}/\text{ml}$) was significantly lower ($p=0.001$) than it was in the controls (8.6 ± 1.8 $\mu\text{g}/\text{ml}$). The malone dialdehyde levels in the COPD patients were significantly higher in both the acute (2.4 ± 0.7 nmol/ml) and the stable phase (1.2 ± 0.4 nmol/ml) ($p=0.001$; $p=0.005$) than they were in the controls (0.9 ± 0.2 nmol/ml).



Conclusion

Patients with COPD undergo increased oxidative stress during exacerbations, which is maintained also in stable periods. At the same time, their serum concentration of vitamins A and E decrease in periods of exacerbation. Therefore the administration of vitamins A and E may be beneficial in the prevention of the harmful effects of COPD.



Oxidative stress and the effects of antioxidants in COPD patients

The effects of antioxidants on exercise-induced lipid peroxidation in patients with COPD
Agacdikien A, Basyigit I, Ozden M, et al. *Respirology* 2004;9(1):38–42.

Study design, patients and methods

Oxidative stress plays an important role in the pathogenesis of chronic obstructive pulmonary disease (COPD). It may be caused by cigarette smoke, environmental pollution, infections and physical exercise. The aim of the present study was to find out whether the daily intake of the antioxidant vitamins E (200 I.U.) and C (500 mg) could reduce the symptoms of oxidative stress within one month.

Twenty-two male patients with stable COPD and 10 healthy controls were included in the study. Ten of the COPD patients were given both vitamins over a period of one month in addition to their normal medication (including anticholinergic drugs, slow-release theophylline and a beta2-agonist). At baseline and one month after study termination all subjects underwent a treadmill exercise test until onset of fatigue, dyspnoea or ECG changes (ST/T wave abnormalities). Blood samples were collected before the treadmill exercise and 1 and 3 h after the exercise test for analysis of malone dialdehyde (MDA), vitamin E and glutathione (GSH) levels.

Results

In the COPD group GSH and vitamin E baseline values were significantly lower than in the control subjects. There was no difference in MDA levels between the two groups. As a result of physical exercise the MDA and vitamin E levels of the COPD patients increased significantly, but not the GSH levels. In the control group, however, the MDA, vitamin E and GSH concentrations were unchanged after the treadmill exercise test. Whereas the untreated COPD patients still had rising MDA and vitamin E levels after physical exercise even one month later, the treated COPD patients did not show any further increase after one month of antioxidant intake.

Prior to the antioxidant treatment the exercise test duration of COPD patients was 5.7 ± 2.1 minutes, for the healthy controls it was 11.3 ± 1.2 minutes. Both parameters increased significantly after antioxidant supplementation of the COPD patients.

Conclusion

Compared to healthy controls, the MDA levels, and thus lipid peroxidation, of the COPD patients increased clearly under physical exercise. After one month of vitamin E and C supplementation in COPD patients there was no increase in MDA levels after physical exercise, and the duration of the exercise test was significantly longer. Thus, antioxidants with their nutritive properties may reduce the harmful effects of oxidative stress.



Unfavorable oxidative status associated with limited pulmonary function

Antioxidants, oxidative stress, and pulmonary function in individuals diagnosed with asthma or COPD
Ochs-Balcom HM, Grant BJB, Muti P, et al. Eur J Clin Nutr 2006.60(8):991–99.

Study design, patients and methods

A total of 218 individuals with chronic airflow limitation and recruited randomly, among them 68 asthmatics, 121 diagnosed with COPD and 29 suffering from both, provided detailed information about their life style and dietary habits. In addition, the pulmonary function of the patients was determined and compared with that of a healthy control group (FEV₁% and FVC%^{*}). The oxidative status was assessed on the basis of the serum levels of various antioxidant vitamins and TBARS (thiobarbituric acid reactive substances) and the erythrocyte glutathion content.

Results

After adjustment for various covariates, a clear correlation was found between the pulmonary function of the subjects examined and their oxidative status. Thus, FEV₁% was significantly associated with the serum levels of beta-cryptoxanthin, lutein/zeaxanthin and retinol and the dietary beta-carotene, beta-cryptoxanthin, lutein/zeaxanthin, vitamin C and lycopin.

A similar association was found to exist for serum levels of beta-cryptoxanthin, lutein/zeaxanthin and lycopene, or dietary beta-cryptoxanthin, beta-carotene, vitamin C and lycopene, and the FVC%. Reversely, a higher glutathion content of erythrocytes was associated with a significantly lower FEV₁% and higher TBARS levels with a significantly lower FVC%.

Conclusion

In asthmatic and COPD patients the reduced pulmonary function is reflected in an imbalance between oxidative and antioxidant substances. In patients with chronic respiratory disease a similarly high dietary intake of antioxidants is apparently associated with lower plasma levels of the respective substances than in healthy individuals. Thus, patients with asthma and COPD may have a greater need for antioxidants due to increased oxidative stress, e.g. as a result of inflammatory processes.

* FEV₁%: = Forced Expiratory Volume in 1 second; FVC% = Forced Vital Capacity, each as a percentage of the predicted value



Antioxidants can support chemotherapy

Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer
Pathak AK, Bhutani M, Guleria R, et al. J Am Coll Nutr 2005;24(1):16–21.

Study design, patients and methods

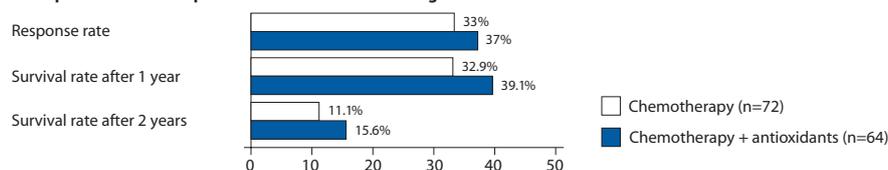
One hundred and thirty-six previously untreated patients with non-small cell lung cancer of stage IIIb or IV received either chemotherapy (n=72) or chemotherapy plus vitamins C, E and beta-carotene (n=64). Patients in both groups were given paclitaxel and carboplatin every three weeks. This cycle was repeated 6 times at most.

The antioxidant group was given a daily dose of 6,100 mg vitamin C, 1,050 mg D₁-alpha-tocopheryl succinate and 60 mg of synthetic beta-carotene. After the end of chemotherapy the antioxidants were gradually reduced to half the amounts, and this dose was maintained until the end of the observation period (2 years). The therapeutic efficacy was assessed at regular intervals on the basis of the clinical and radiological findings.

Results

In a total of 323 or 301 treatment cycles, respectively, 33% of the patients responded to chemotherapy alone (24/72, partial remissions only), and in the group receiving chemotherapy plus antioxidants the percentage of responders was 37% (24/64), including two complete remissions. Overall survival rates after one and two years amounted to 32.9% and 11.1% (only chemotherapy) vs. 39.1% and 15.6% (chemotherapy plus antioxidants), the mean survival time was 9 vs. 11 months in the chemotherapy vs. chemotherapy + antioxidants group. The results all of which were more favorable for the combination therapy were not statistically significant. The adverse effects of chemotherapy were similar in the two groups.

Therapeutic outcome in patients with non-small cell lung cancer



Conclusion

The concern that antioxidant vitamins would protect cancer cells and therefore jeopardize the efficacy of standard chemotherapy, was not supported in this trial conducted with patients who suffered from advanced non-small cell lung cancer. On the contrary, antioxidant supplementation rather had a favorable influence on the course of therapy in such cancer patients. However, the effect observed did not reach the level of significance.



Folic acid can slow down tumor progression to laryngeal cancer

Pilot phase IIA study for evaluation of the efficacy of folic acid in the treatment of laryngeal leukoplakia
Almadori G, Bussu F, Navarra P, et al. Cancer 2006; [Epub ahead of print].

Study design, patients and methods

Forty-three patients affected by premalignant laryngeal leukoplakia were enrolled in the pilot study. This disease consists of a hyperplasia of the laryngeal mucosa which frequently degenerates to a malignant tumor. The patients had varying degrees of severity of laryngeal leukoplakia. The tissue samples showed either normal mucosa, hyperplasia or various stages of dysplasia at the leukoplakia sites. The patients took 5 mg of folic acid three times per day over a period of 6 months, without any further medical treatment. Every 30 days the patients underwent a videolaryngoscopy. In addition, the serum folate and homocysteine levels were measured.

Results

In 31 of the 43 patients assessed (72%) the tissue alterations had decreased in size after treatment with high doses of folic acid by at least 50% or had completely disappeared.

In all, 12 patients (28%) experienced complete remission of the premalignant laryngeal leukoplakia.

In 19 patients (44%) leukoplakia had receded by more than 50%, and in 12 patients (28%) no improvement of the tissue alterations was observed (non-responders). If those individuals who had a healthy mucosa at the beginning of the trial are excluded from the non-responders, the number of patients not showing any improvement decreases from 12 (28%) to 7 (16%).

Correspondingly, the number of patients who experienced a reduction of leukoplakia and/or complete remission increases to 50% and 31%, respectively. Moreover, a significant increase in serum folate levels (from 5.19 ng/ml to 10.06 ng/ml; $p < 0.0001$) and a significant reduction in homocysteine concentrations was measured (from 10.9 $\mu\text{mol/l}$ to 3.65 $\mu\text{mol/l}$; $p = 0.001$).

Conclusion

In 33 (72%) of the 43 patients examined the premalignant laryngeal leukoplakia decreased in size by at least 50% or even disappeared completely after administration of folic acid. According to the researchers, folate supplementation could be an option for secondary prevention in such high-risk patients.



Supplementation of antioxidant vitamins can enhance the efficacy of standard cancer therapy

High doses of multiple antioxidant vitamins: essential ingredients in improving the efficacy of standard cancer therapy
Prasad KN, Kumar A, Kochupillai V, et al. J Am Coll Nutr 1999; 18(1):13–25.

Study design, patients and methods

In this review article, in-vitro and in-vivo studies assessing the effect of antioxidant vitamins (such as vitamins A, E, C) and carotenoids on tumor progression are summarized.

Results

In rodent and human cancer cells, treatment with antioxidant vitamins (vitamins A, C, E) and 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 inhibition of the protein kinase C) and lead to a reduction of oncogene expression (such as c-myc and H-Ras). In addition, vitamin E increases the formation and release of the growth inhibitor TGF- β and reduces phosphorylation and activity of the transcription factor E2F which has a central role in cell proliferation. Individual antioxidant vitamins or the combination of several vitamins enhance the growth inhibiting effect of radiotherapy, chemotherapy and hyperthermia treatment. Healthy body cells seem to accumulate much lower antioxidant levels than cancer cells which means that healthy cells are protected against the growth inhibiting effects of standard cancer therapy, whereas the high antioxidant levels in the cancer cells induce the growth inhibiting signals mentioned as well as differentiations. As a result of this selective effect, the toxicity of tumor therapeutic agents can be reduced.

Conclusion

The author concludes that antioxidants with their nutritional characteristics can

- enhance the efficacy of chemotherapy, radiotherapy and hyperthermia treatment,
- reduce the expression of oncogenes in cancer cells,
- induce cancer cell differentiation, and
- mitigate the toxicity of cancer therapy.



The immune system feels the difference

Micronutrients

- immune-specifically composed
- balanced dosages

Important micronutrients	Features and characteristics
Antioxidant vitamins (such as vitamin A, C, E) and carotenoids	<ul style="list-style-type: none"> → scavenge free radicals and eliminate / neutralize them → support immune defences → enhance cell protection
Bioflavonoids	→ as natural antioxidants support the effect of vitamin C
Trace elements (such as zinc, selenium)	→ essential for many functions of the immune system
B vitamins	→ important for the energy metabolism



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