Nutritional support for the immune system

by Robert A. Ronzio, Ph.D.

How can we avoid colds, flu, and bacterial infections that seem inevitable each winter? Recent advances emphasize that specific nutrients are critically important for both humoral and cell-mediated responses of the immune system.[1] Humoral responses rely on antibodies and the complement system. B-lymphocytes triggered by a given antigen proliferate and form mature plasma cells, which in turn produce large amounts of antibodies. On the other hand, cell-mediated immunity relies on T cells to regulate other defensive cells, including macrophages (large phagocyte cells) and circulating phagocytic cells, especially neutrophils. T cells release a variety of lymphokines to orchestrate both cell-mediated and antibody-mediated responses.

With so many different components, it is not surprising the immune system requires multiple nutrients. Cells of the immune system generally turn over rapidly, accentuating high nutrient requirements. Inflammation generates free radicals and other reactive chemical species that increase the oxidative burden of the body and exhaust antioxidants. If unchecked, they damage membrane lipids, impair T-cell function, and injure tissues. Consequently, a wide variety of antioxidants are needed to protect immune system cells.

This review focuses on key nutrients and important dietary factors. Space limitations preclude a discussion of other aspects of immune support, including goldenseal, garlic, echinacea, astragalus, hydrastis, as well as various polysaccharides. Nutrient levels are discussed in the context of support for sub-par immune functioning. Generally, such levels are not readily obtained from foods or typical "one-a-day" multivitamin/mineral pills. Extra nutritional supplements, adjusted for individual needs, may be appropriate.

Vitamins

Vitamin A. Vitamin A (retinol) maintains the immune system and lymphatic tissue, and a deficiency can lead to infection. The efficacy of vitamin A in decreasing mortality and morbidity due to various infectious diseases was evaluated by meta-analysis of 12 randomized trials.[2] For example, vitamin A treatment was associated with a 79% reduction in respiratory disease in children. Vitamin A helps maintain the thymus gland and responses of cellular immunity to challenge it. It also supports antibody production, especially secretory IgA.[3,4] Thus, phagocyte activity of circulating polymorphonuclear lymphocytes decreased in vitamin A-deficient lab animals.[5] Vitamin A maintains the integrity of epithelial cells, essential for a healthy mucosal barrier—a non-specific host defense. In vitamin A-deficient animals, the mucosa, glands, and ducts were more susceptible to disease.[3]

Recent studies indicate that vitamin A requirements are only partially met by the consumption of dark green, leafy vegetables—supporting a dietary need for preformed retinol.[6] Typically, vitamin A supplementation in the range of 5,000 to 20,000 IU/day has been used prophylactically, with larger amounts used for several days. Note that vitamin A is a potent teratogen, and the daily intake of supplemental vitamin A for pregnant women, or women who may become pregnant, should not exceed 5,000 IU/day.

Vitamin E. Diets that rely on highly processed, fatty foods may not supply enough vitamin E to ensure long-term health and antioxidant protection, nor do low-fat diets provide adequate vitamin E unless supplemented. Together with glutathione and carotenoids, vitamin E contributes to a dynamic antioxidant defense system.[7] Vitamin E quenches free radicals in cell membranes and serum lipoproteins. Because vitamin E can decrease prostaglandin synthesis, it helps limit inflammation as well.[8] Extra vitamin E can enhance immune function in humans and in animals.[9]

A variety of data suggest elderly people need more vitamin E than younger people. When healthy, elderly volunteers consuming a typical diet were supplemented with extra alpha tocopherol, several indices of cell-mediated immunity improved, including increased delayed type hypersensitive skin response and increased antibody titer to challenge.[10] It is of interest that a maximum response was obtained at 200 mg/day, while 60 or 800 mg/day were less effective.

Natural, mixed tocopherols that include gamma tocopherol may offer additional protection against reactive nitrogen species produced during chronic inflammation.[11]

Vitamin C. A major antioxidant in the bloodstream, vitamin C scavenges free radicals directly, thus combatting oxidative stress. Vitamin C collaborates with vitamin E and coenzyme Q10 as part of an integrated antioxidant defense to protect membranes.[12] To underscore this point, a recent study demonstrated that vitamin C deficiency promoted widespread damage to membrane proteins in guinea pigs, an effect fully reversed by adequate dietary vitamin C.[13] Vitamin C can reduce inflammation, for example, by neutralizing histamine.

Numerous studies have shown that vitamin C is required for a healthy immune system. Vitamin C promotes interferon production, increases chemotoxis and phagocytosis, and enhances T-cell-mediated immunity. Mild ascorbic acid deficiency in volunteers fed five to 20 mg/day for approximately three months reduced delayed hypersensitivity responsiveness and led to a 50% drop in leukocyte vitamin C.[14] Volunteers supplemented with

60 mg/kg vitamin C as a single dose exhibited increased natural-killer-cell activity for more than 24 hours.[15] Indeed, vitamin C itself possesses bactericidal and antiviral properties. A number of studies have documented the benefits of vitamin C supplementation with various infections, such as 200 mg/ day for elderly patients with severe respiratory infections.[16] Gram quantities have been used with AIDS patients.[17]

B complex

Vitamin B_6. Several B vitamins are closely linked to the health of the immune system. Transaminases require vitamin B_6, as pyridoxal phosphate, to break down most amino acids for energy and important precursors. As such, vitamin B_6 plays a critical role in rapidly dividing cells, including those of the immune system. Suboptimal vitamin B_6 consumption may contribute to a defective immune response,[18] perhaps through its role as a cofactor in the formation of cysteine, required for glutathione synthesis. Glutathione in turn functions as a major endogenous antioxidant, important for lymphocyte proliferation. In human as well as animal studies, vitamin B_6 deficiency slowed T-cell differentiation, reduced delayed hypersensitivity responses, impaired antibody production, and reduced neutrophil and macrophage activities.[19] Supplementing with up to 50 mg daily improved lymphocyte subpopulations and mitogen responsiveness in patients who had no evidence of vitamin B_6 deficiency.[20] In addition, pantothenic acid, niacinamide, thiamine, and riboflavin play pivotal roles in energy production essential for humoral and cell-mediated immune responses and a healthy thymus gland.[21] Riboflavin with vitamin B_6 maintains glutathione status.

Folic acid and vitamin B_{12}. Folic acid and vitamin B_{12} are required for DNA synthesis and cell proliferation. As examples, vitamin B_{12} deficiency impaired the complement system[22] and accelerated the development of AIDS symptoms.[23] Folic-acid deficiency decreased thymic function and reduced blastogenic response of T cells.[24] In animals, folate deficiency reduced antibody response. In addition, methyl donor-deficient diets, with inadequate methionine, choline and folate, caused DNA damage and immune dysfunction.[25] Protocols often specify 400 mcg to several thousand mg of folic acid daily. However, large amounts of folic acid can exacerbate deficiencies of zinc and vitamin B_{12}, interfere with dilantin, and may sabotage a lab test used to diagnose B_{12}-deficiency anemia.

Trace minerals

Zinc. This mineral is critically important for normal function of immune cells. Zinc is a required cofactor for enzymes such as DNA and RNA polymerases, essential for cell proliferation. As a cofactor of cytoplasmic superoxide dismutase, the only enzyme designed to specifically inactivate free radicals, zinc functions as an antioxidant. Immune cells—including granulocytes—require zinc for chemotaxis.[26] Zinc deficiency can cause atrophy of lymphoid tissue with decreased T cell, neutrophil, and phagocytic responses, decreased skin-delayed hypersensitivity response, lowered secretory IgA production, and less thymic hormone responsiveness.[27] Furthermore, zinc supplementation (45 mg/day) for 30 days reduced the incidence of infection and increased the production of T-helper cells over a two-year period for patients with Stage III and IV HIV infections.[28] On the other hand, excessive zinc reduces immune function, perhaps by competing with copper.[29] Extra copper is needed when large amounts of zinc are ingested.[30]

Selenium. Selenium forms the active site of glutathione peroxidase, a class of enzymes that detoxify cytoplasmic hydrogen peroxide and reduce fatty-acid peroxides in membranes. Selenium also enhances the antioxidant properties of vitamin E. In this sense, selenium can be considered an antioxidant. Erythrocyte glutathione peroxidase was found to be significantly higher in younger people than in well-nourished elderly subjects, reflecting an age-related decline in certain antioxidant defenses.[31] Inadequate dietary selenium can cause depressed immunity and reduced T-cell production in humans and animals.[32] Supplementing healthy, elderly persons with trace minerals, as well as vitamins, may improve various immune indices.[33] A study of 125 HIV-positive people over 3.5 years indicated that selenium deficiency was strongly correlated with disease mortality.[34] Recommendations in usual supplementation schedules range from 50 to 250 mcg daily.

Other dietary factors

Essential fatty acids. Consuming several grams of long-chain n-3 polyunsaturated fatty acids (PUFA) can ameliorate inflammatory conditions such as lupus and rheumatoid arthritis.[35] Consuming PUFA to counter inflammation and support cardiovascular health needs to be balanced against potential immunosuppression. Both n-3 and n-6 PUFA can inhibit antigen/mitogen-stimulated lymphocyte proliferation.[36] A large body of evidence suggests that changes in eicosanoid synthesis[37,38] mediate the effects of n-3 PUFA on the immune system. Thus, n-3 PUFA inhibit proinflammatory leukotriene B_4 and increase production of leukotriene B_5 to counter inflammation.[39] Increasing PUFA intake without increasing vitamin E can suppress the immune response in those consuming high-fat diets.

When alpha-linolenic acid (flaxseed oil) supplied 6% of energy for 56 days, lymphocyte proliferation in response to mitogens was inhibited in healthy young men.[40] However, increased vitamin E intake eliminated the inhibition of lymphocyte proliferation by fish-oil supplementation.[41] The net effect of fatty acids and fat on the immune response depends upon the total dietary fat, the type of fat consumed, and the ratios between different fatty acids, their chain length, and degree of unsaturation. Supplementing 2 g of n-3 fatty acids per day, equivalent to 100 to 200 g of oily fish, has been recommended for immune support.[42] The optimal ratio for n-6 PUFA: n-3 PUFA may be in the range of 4:1—far less than the typical US diet supplies.

Coenzyme Q10. Coenzyme Q10 (CoQ10) functions both as a mitochondrial electron carrier, essential for energy production, and as a lipid-soluble antioxidant capable of regenerating vitamin E.[43] Supplemental CoQ10 both increases plasma levels of CoQ10, and decreases the formation of lipid peroxides in plasma.[44] This coenzyme becomes a conditionally essential nutrient when synthesis declines with age, nutrient deficiency, or infection. Animal studies have been revealing: Supplemental CoQ10 was shown to increase both phagocytosis and antibody levels in lab animals.[45] CoQ10 levels declined in aging mice, and additional CoQ10 reversed several indices of aging.[46] Together with vitamin B_6, CoQ10 supported the production of T4-lymphocytes and increased IgG levels in human subjects.[47]

As with other lipid-soluble nutrients—such as vitamins A and E—efficiency of uptake is an important consideration. Emulsified CoQ10, supplemented at a level of 30 mg daily for 30 days in healthy volunteers, increased plasma levels approximately three-fold more than usual forms of CoQ10.[48] Those individuals with the lowest baseline CoQ10 levels experienced the largest increases. In nutritional protocols, recommended CoQ10 supplementation ranges from 10 to 100 mg or more per day.

Carotenoids. Hydrocarbon carotenoids, such as alpha- and beta-carotenes, or oxycarotenoids—including zeaxanthin, lutein, and cryptoxanthin—complement vitamin E as lipid-soluble antioxidants that limit lipid peroxidation.[49] In general, carotenoids enhance thymic function and antibody production, and they enhance interferon activity in older animals.[50] Healthy male nonsmokers supplemented with 60 mg of beta-carotene for nine months exhibited increased CD4/CD8 ratio compared to placebo controls, although NK cells and cytotoxic T cells were unaltered.[51] In a similar group of subjects, supplementation with 15 mg of beta-carotene increased blood monocyte expression of major histocompatibility complex class II proteins, making them more efficient in initiating an immune response.[52] When healthy volunteers were administered 180 mg beta-carotene/day for 14 days, helper/inducer T cells increased by 30%, raising the possibility of increasing immunologic competence in those conditions with characteristically low T4 subsets.[53]

Nonetheless, it seems prudent to include protective antioxidants such as vitamin E with beta-carotene to diminish possible problems in using beta-carotene alone.[54] Natural mixed carotenoids are better absorbed and function as more effective antioxidants in humans than synthetic beta-carotene.[55]

Flavonoids. Polyphenolic phytochemicals inhibit inflammation through a variety of mechanisms. Flavonoids are versatile antioxidants; they can also stabilize vitamin C. Quercetin, probably the most extensively studied example, reduces mast-cell degranulation, thus limiting the release of proinflammatory agents.[56] Many flavonoids can inhibit cyclooxygenase and lipoxygenase, enzymes that convert arachidonic acid to prostaglandin PG2 and leukotrienes.[57]

Oligomeric proanthocyanidins stabilize endothelial membranes and inhibit the respiratory burst that activated macrophages generate. They also scavenge nitric oxide and inhibit the up-regulation of nitric-oxide synthase by activated macrophages.[58] A recent study demonstrated that polyphenols from nonsoy legumes, shown to be highly effective superoxide scavengers,[59] trigger apoptosis in cultured macrophages, while preventing peroxynitrite-induced apoptosis in colonic epithelial cells.[60] Potentially, such polyphenols may help normalize intestinal function during gut inflammation.

Nutritional support for the thymus gland

The thymus gland plays a central role in balancing the immune system. It directs the production and maturation of lymphocytes, including T suppressor, T helper, cytotoxic T cells, and natural killer cells. Thymic stem cells mature under the influence of thymic hormones, particularly thymosins and thymopoietin. Thymic hormones and factors are often low in those with compromised immune systems.

The thymus gland increases in size throughout childhood, reaching a maximum at puberty. Subsequently, the gland undergoes involution. As the cortex and medulla decrease in size, fat infiltration increases some 10- to 20-fold. Antioxidants described earlier may help reduce oxidative damage in the thymus, while zinc and vitamin B_6 support the production of thymic hormones.

Orally administered bovine thymus preparations offer another approach to immune support. Thymus glandulars provide factors that support normal function.[61,62] Thymus extracts can help normalize elevated and depressed ratios of T-helper/T-suppressor cells.[63] Bovine thymosin and thymic extract reduced the incidence of infection.[64] Calf thymus extract, administered to mice at 10 mg/kg body weight, reversed immunosuppression caused by physical stress.[65]

Thymic preparations of glands from young (neonatal) animals are desirable for several reasons. The thymus gland exhibits maximal growth rate after birth, when it produces elevated levels of factors to program T cells. Compared to the adult tissue, neonatal thymus has not been subjected to life-long exposure to pollutants and environmental stressors, and it is particularly enriched in cortical cells with little of the fatty infiltration found in the adult gland. Other glandular support for the immune system includes adrenal gland, spleen, liver, parotid, and lymphatic tissues.

Final comments

In summary, natural compounds such as vitamins, trace minerals, essential fatty acids, CoQ10, flavonoids, carotenoids, and thymus glandulars can strengthen the immune system and lower the odds of recurrent infections. Balanced supplements are essential: excessive amounts of zinc, selenium, vitamin A, or vitamin E reduce immune responses.[66]

However diet and nutrition are only one piece of the health puzzle. A prudent lifestyle emphasizing plenty of rest, effective stress management, exercise, and a positive mental attitude are also essential for optimal immune functioning.

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