Essential nutrients and immunologic functions

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ABSTRACT Several indexes of immune response, including responses on delayed-type hypersensitivity skin tests, antibody production, lymphocyte proliferation, cytokine production, and numbers of the specific subgroups of white blood cells, are influenced by essential nutrient intake and may serve as functional tests for evaluating nutritional status. In certain segments of the population, such as elderly persons and smokers, activity of the immune indexes can be increased through dietary supplementation with micronutrients, and there may be a rationale to increase selected recommended dietary allowances for the general population. The activity of the immune system may also be enhanced with decreases in total fat intake or lessened with increases in total fat intake, particularly of the n-3 type. Research to date, therefore, suggests that several dietary components, both essential and non-essential, can affect human immune response. The intake of these nutrients can be modulated to regulate the activity of the immune system. Am J Clin Nutr 1996:63:994S–6S

KEY WORDS Vitamin C, vitamin E, β-carotene, dietary fat, n-3 fatty acids, n-6 fatty acids, cell-mediated immunity

INTRODUCTION

Initial evidence linking malnutrition and poor immune status came from historical accounts of famines and pestilence and epidemiologic studies. Scrimshaw et al (1) reviewed the literature linking malnutrition and immune response in 1959 and reported, “many of the important infections of human populations are rendered more serious in their consequences by the presence of malnutrition; that a few infections are indeed less severe when associated with nutritional deficiency; and that many infections themselves precipitate nutritional disturbances.” Beisel (2) coined the acronym NAIDS to depict nutritionally acquired immune deficiency syndrome and reported that a combination of infection and malnutrition in children with NAIDS accounted for > 40 000 deaths/d in underdeveloped countries, plus countless other deaths of adults with NAIDS in modern hospitals. Several other chronic diseases including cardiovascular disease, cancer, and arthritis also have their roots in disorders of the immune system; the course of these diseases can be altered by nutritional interventions. Several nutrients, including vitamins, minerals, and amino acids, influence the activity of immune cells. Of the several books written on this topic, we refer to two of the most recent (3, 4); this article is restricted to the effects of dietary lipids and antioxidant nutrients on immune response.

EFFECTS OF VITAMINS C AND E AND β-CAROTENE ON HUMAN IMMUNE RESPONSE

Several recent, well-controlled human intervention studies found that clinically important immune responses were improved when amounts of vitamin C, vitamin E, or β-carotene higher than the recommended dietary allowance (RDA) were consumed in healthy populations (5). For example, in a placebo-controlled, double-blind intervention study conducted in a metabolic ward, responses on delayed-type hypersensitivity (DTH) skin tests, an important index of overall immune function, were significantly reduced in a group of healthy men when their vitamin C intake was reduced from 250 to 5, 10, or 20 mg/d for 60 d, even though lymphocyte proliferation in vitro was not affected (6). DTH responses did not return to baseline when vitamin C intake was increased to 60 mg/d (the current RDA) or to 250 mg/d for 3 wk. DTH responses may have returned to baseline if the duration or amount of vitamin C supplemented during the repletion phase was increased. In another placebo-controlled, double-blind study, incidence of postrace infections in marathon runners was twice as great in those not taking vitamin C supplements compared with runners who took ~1 g vitamin C/d (7). Data from a large national survey found that forced expiratory lung volume, a clinically important index of lung function, was significantly greater in individuals consuming ~178 mg vitamin C/d compared with those consuming the RDA for vitamin C (8). The data discussed clearly show that supplemental amounts of vitamin C can be beneficial and can improve certain indexes of human immune responses.

Lifestyle and environmental factors can adversely affect both the status of essential nutrients and immune responses. For example, tissue concentrations of vitamin C, vitamin E, β-carotene, vitamin B-6, and folate are lower in smokers than the corresponding values in nonsmokers. Smokers have elevated neutrophil-oxidation activity, which may reduce antioxidant-nutrient status. In one trial, the activity of neutrophils from

1 From the US Department of Agriculture, Agricultural Research Service, Pacific West Area, Western Human Nutrition Research Center, Presidio of San Francisco; and Hoffmann-La Roche Inc, Paramus, NJ.


3 Reference to a company or product name does not imply approval or recommendation of the product by the US Department of Agriculture to the exclusion of others that may be suitable.

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smokers was reduced to normal with β-carotene supplementation (40 mg/d) (9). In a separate study, supplementation (30 mg/d) reduced the number of precancerous oral leukoplakia lesions, and at the same time, natural killer (NK) cell functions were significantly enhanced (10). Exposure to ultraviolet light decreases circulating β-carotene concentrations as well as reduces DTH responses. Supplemental β-carotene (30 mg/d) reversed these two effects of ultraviolet light in healthy volunteers (11). β-Carotene supplementation appears to be beneficial for individuals with compromised immune systems, and does not overstimulate the immune responses of healthy adults, which were not lowered by β-carotene depletion (9, 10, 12).

The elderly are another group at risk for decreased immune responses. In fact, DTH responses at the time of hospitalization of elderly persons can be used to predict death; the incidence of death was 30 times greater in those with negative responses to all seven recall antigens compared with those who had at least one positive response (13). Thus, it is clinically important that DTH responses in healthy elderly persons were increased significantly with vitamin E supplementation (60, 200, or 800 mg all-rac-α-tocopherol acetate/d) for 6 mo (14). DTH responses were also significantly enhanced in a separate placebo-controlled study in which healthy elderly subjects took a multivitamin and mineral tablet (Theragra-M; Bristol-Myers Squibb Company, New York) for 1 y (15). In a third study in Newfoundland, Canada, Chandra (16) showed a significant decrease in the number of sick days and in use of antibiotics, as well as an increased antibody response to the flu vaccine, in a group of healthy elderly subjects who supplemented their diets with a multivitamin supplement that contained 100% of the RDA of most vitamins and moderately higher amounts of vitamin C (80 mg/d), vitamin E (44 mg/d), and β-carotene (16 mg/d). Note that the dietary habits of the elderly in all three studies were assessed by the authors, who indicated that the diets were not deficient in any micronutrient and contained approximately the recommended amounts of all micronutrients. Thus, it appears that to maintain their immune responses at an optimum, healthy elderly persons may need amounts of certain essential micronutrients higher than their usual dietary intake and the current RDA, and higher than amounts needed by younger adults.

**DIETARY LIPIDS AND IMMUNE RESPONSE**

In the past decade, several studies have been conducted to examine the effects of amount and type of dietary fat on human immune response. In two separate studies conducted in a metabolic suite, the proliferation of peripheral blood lymphocytes increased significantly in men and women in response to mitogens specific for T and B cells when the fat content of the diets was reduced from 30% or 40% of energy to 25% of energy (17, 18). The range of n–6 PUFAs (3–13% of energy) tested in these studies did not affect lymphocyte proliferation or several other indexes tested. An increase in lymphocyte proliferation and the secretion of interleukin 1 (IL-1) was also observed in a group of elderly subjects when fat intake was reduced from 36% to 27% of energy (19). The lowering of fat intake from 32% to 22% of energy increased NK cell activity in a group of healthy men (20). This increase in NK activity was prevented by the daily additional intake of 15 g safflower oil but not coconut oil. A study conducted with elderly Danish men showed an inverse correlation between NK cell activity and serum concentrations of PUFAs (21); however, no correlation was detected between NK cell activity and adipose tissue PUFA profiles of young American men (22). These studies indicated an increase in several indexes of immune response when the percentage of energy from fat was decreased. Whether n–6 PUFAs are more inhibitory than saturated fatty acids, as seen in animal studies, is not clear from the limited studies conducted in humans. The available data suggest that a moderate increase in the intake of n–6 PUFAs in a diet containing >30% of energy from total fat and with adequate amounts of antioxidant nutrients should not have any adverse effects on immune response. However, such an increase may suppress immune response in individuals with low antioxidant-nutrient status who are consuming high-fat diets (21).

Because of the recommendations made by some groups that the intake of n–3 PUFAs should be increased to improve cardiovascular health, several studies have been conducted in the past few years to examine the effects of these fatty acids on immune response. Lymphocyte proliferation in response to T cell mitogens and DTH response were inhibited when 10 healthy male soldiers supplemented their diets with flaxseed oil to provide 6% of energy from α-linolenic acid for 56 d (23). Adding 18 g fish oil, equivalent to 5 g eicosapentaenoic acid plus docosahexaenoic acid, to the diets of nine healthy subjects for 6 wk inhibited several indexes of immune response including neutrophil chemotaxis and secretion of IL-1, IL-2, and tumor necrosis factor (24, 25). All these indexes returned to baseline 20 wk after the discontinuation of fish oil supplementation, although many remained inhibited 10 wk after discontinuation. These and many other studies indicate that many indexes of immune response are inhibited by supplementation with fish oils, and the time taken for the inhibition to occur or for it to be overcome after discontinuation of fish oil supplementation varies with the different indexes of immune response. Inhibition of lymphocyte proliferation caused by fish oil supplementation could be overcome with increased intake of vitamin E (26).

Oxidative responses of neutrophils isolated from human type IV hyperlipidemic patients [elevated very-low-density lipoprotein (VLDL)] are decreased compared with responses of neutrophils from normal subjects (27). In vitro studies indicate that VLDL and low-density lipoprotein (LDL) inhibit lymphocyte and neutrophil functions, whereas high-density lipoprotein (HDL) stimulates neutrophil functions (28, 29). Results of other in vitro studies indicate that it is not pure cholesterol but oxysterols and apoproteins B and E that inhibit lymphocyte functions (30, 31).

The net effect of dietary fat on immune response is an outcome of the interaction and balance between several factors including total fat, type of fat, the ratios between different fatty acids, chain length, degree of unsaturation, duration of feeding, and antioxidant-nutrient status. Because several other micronutrients can affect immune status, indexes of immune response cannot be used to detect essential fatty acid nutritional status except under rare deficiency conditions; however, the amount of total fat in the diet and the ratios between different fatty acid classes can be used to modulate human immune response. The existing immunologic data support the current recommendations by the American Heart Association to de-
crease fat intake to 30% of energy with 10% of energy each from saturated, monounsaturated, and polyunsaturated fatty acids. On the lower end, ≥ 20% of energy from fat is needed for health maintenance and efficiency in healthy adult populations (32).

CONCLUSIONS

Immune responses can be changed by altering the intake of several essential micro- and macronutrients. For certain segments of the population, the concentration of some of the nutrients required to attain the highest activity of the immune indexes appears to be greater than the current RDAs. These segments of the population may benefit from supplementation. Further studies are needed to determine the responsiveness of different indexes of immune response to changes in nutrient intake and to compare such indexes with those used to determine the current RDA. Because many nutrients interact with one another, understanding their combined effects on immune responses requires additional studies. It appears that future micronutrient recommendations may have to take into account new indexes, such as immune function.

REFERENCES