

## Mini Review

## Potential role of nutrients on immunity

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Received: 27 November 2014

Received in revised form:

9 May 2015

Accepted: 15 August 2015

**Abstract**

The immune system protects the host against pathogenic organisms and acts to ensure tolerance to self, to food and environmental components. Bovine milk, micronutrients and many nutrients beneficially affect the host immunity. Bovine milk has many components that improve the body immune functions. In addition, a significant mass of research now exists investigating the role of probiotic and prebiotic in ameliorating immunity during various intestinal diseases. Vitamins and minerals boost immunity. Micronutrient deficiency suppresses immune function by affecting the innate T-cell mediated immune response and adoptive antibody response. Moreover essential fatty acids, and some amino acids have numerous important influences on immune responses. Besides, glutathione and nucleotides are important components of immunonutrient mixes. Also, in this article, an overview of how nutrient-nutrient interaction may affect host immunity, was discussed.

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**Keywords**

Immunity

Probiotic

Prebiotic

Micronutrients

Fatty acids

Amino acids

**Introduction**

Immune function protects healthy tissue from disease promoting factors. Nutrient availability has the potential to affect all aspects of the immune system. In general, deficiency of several nutrients will lead to impaired immune responses, and replenishment of those specific components will typically restore the affected responses (Fernandes *et al.*, 2006). In human beings, nutrient deficiencies impaired the immune response. Besides, conditions associated with over nutrition such as cardiovascular disease (Kang *et al.*, 2001), diabetes and obesity significantly modulate immune function (Chandra, 2002). Furthermore, nutrients are involved in the stability of the plasma membrane and the differentiation and expression of its cell surface characteristics such as antigenic determinants. Also, nutritional factors modulate metabolic processes which may include the activation or inhibition of key enzymes or immunoregulatory mediators that can result in altered cellular immune function particularly in cells of T lymphocytes lineage (Broome *et al.*, 2004). Deficiency of single nutrient also results in altered immune responses; this is observed even when the deficiency state is relatively mild. Of the micronutrients, zinc, selenium, iron, copper, vitamins A, C, E, and B<sub>6</sub>, and folic acid have important influences on immune responses (Chandra, 1997).

*Immunity and immune system*

The immune system is made up of a vast and highly complex net work of cells, tissues and organs that all work in union all of the time to protect the body from harm. If an individual has impaired immunity, the body's natural defenses could quickly be overwhelmed, resulting in serious infection, illness, and even death (Fritsche, 2006). Immunity may be innate (non specific) or acquired (specific). Innate immunity is conferred by all elements with which an individual is born and which are available at a very short notice to protect the individual from challenges by foreign invaders. Acquired immunity is more specialized than innate immunity and it supplements and augments the protection provided by innate immunity. It is acquired by contact with the invader and is specific to it only (Benjamini *et al.*, 2000). Two major cell types are involved in acquired immunity. During ontogeny the bone marrow provides stem cells that will develop in situ into lymphocytes of the  $\beta$  lineage and in the prenatal thymus into lymphocytes of the T lineage. These cells mature and leave the bone marrow and thymus to populate the lymphoid organs and the circulatory system.

Beta cells are activated to secrete antibodies after the binding of antigens to Ig. Acquired immunity mediated by  $\beta$  cells and antibodies is called humoral immunity. Besides, cellular or cell mediated immunity

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is mediated by T cells which synthesize and release various cytokines and interferon- $\gamma$  (INF- $\gamma$ ) that affect other cells (Benjamini *et al.*, 2000). T cells may exert a helper, suppressor or effectors function. Macrophages have antigen physically on their surface and bind directly to T cells. They also produce cytokines as interleukin-1 (IL-1), interleukin-12 (IL-12), tumor necrosis factor - $\alpha$  (TNF- $\alpha$ ) that assist in the activation of T-cell. Macrophages also produce arachidonic acid metabolites such as prostaglandin-E<sub>2</sub> which can down regulate T-cell functions. Macrophage in turn can be activated by T-cell cytokines as IFN- $\gamma$  to become more effective in controlling intracellular pathogen. Macrophages and polymorphonuclear neutrophil (PMN) can bind and internalize antigen (as bacteria and virus) coated with antibody and/or other proteins and destroy them (Kubena and McMurray, 1996). The natural killer cell (NK) is an additional cell type that plays an important accessory role in the immune response. NK cells produce cytokines such as IFN- $\gamma$ , which can regulate macrophages. In turn, NK activity can be enhanced by IL-12 and IL-2 produced by other immune cells.

Lymphoid organs are those organs in which lymphocyte maturation, differentiation and proliferation take place. They are divided into primary or central lymphoid organs in which T and  $\beta$  cell maturations take place. Mature T and  $\beta$  lymphocytes migrate from thymus and bone marrow, respectively, through the blood stream to peripheral lymphoid tissues, including the lymphnodes, spleen and gut associated lymphoid tissue such as the tonsils. The secondary lymphoid organs are those organs in which cell proliferation and differentiation take place (Rich *et al.*, 2001).

#### *Milk as unique source of immunomodulatory ingredients*

The components of milk contribute to health both directly and indirectly. Milk has many components that have been shown to influence the immune function (Li *et al.*, 2014). The majority of immunomodulatory activity of bovine milk has been detected in milk proteins (casein and whey) and milk fat. Bounous *et al.* (1983) have demonstrated that the whey protein and  $\alpha$ -lactalbumin could dramatically enhance lymphocyte function when included in a dietary formulation fed to mice. They can also enhance the responsiveness of spleen derived lymphocytes to T cell mitogens (Wong and Watson, 1995). Both lactoferrin (LF) and K-casein derived caseinoglycopeptides (CGP) have been shown to enhance lymphocyte function (Sfeir *et al.*, 2004). Peptides derived from the enzymatic cleavage of  $\alpha$

and  $\beta$ -casein have been shown to suppress mitogen stimulated proliferation of human lymphocytes *in vitro* (Kayser and Meisel, 1996). Sutas *et al.* (1996) have shown that peptides derived from the enzymatic cleavage of K-casein can enhance human lymphocyte function *in vitro*. Brosche and Platt (1995) have shown that elderly subjects had enhanced blood cell phagocytic function following consumption of milk based diet.

Dietary inclusion of the fatty acid conjugated linoleic acid (CLA), a milk fat derived component has been shown to enhance *in vitro* lymphocyte proliferation as well as lymphocytes responses (Chew *et al.*, 1997). In addition to affecting lymphocyte function, dietary milk proteins have been shown to modulate antibody responses (Ambroziak and Cichosz, 2014). Alfa-lactalbumin,  $\alpha$ -lactalbumin hydrolysate and whole whey protein concentrate have each been shown to enhance antibody production to foreign antigen (Bounous *et al.*, 1981). Cloistral whey derived extract produced lower IgE antibody responses to foreign antigen. This is a benefit, where the development of IgE antibody responses can lead to allergic hypersensitivity reactions. Further research has demonstrated that both K-casein and lactoferrin can suppress IgE mediated hypersensitivity responses by inhibiting histamine release (Otani and Yamada, 1995). Moreover dietary whey protein concentrate can enhance intestinal mucosal antibody responses against orally administered cholera toxins (Cross and Gill, 2000). Also, whey proteins can promote overall weight gain in human immunodeficiency virus (HIV) positive men (Bounous *et al.*, 1983), to increase tissue concentrations of glutathione which promotes cellular immune function (Bounous and Gold 1991) and to inhibit viral binding to cell surface receptors on T lymphocytes in HIV patients (Neurath *et al.*, 1996). In addition, bovine milk contains high concentration of immunoglobulins (Goddeeris and Morrison, 1994). Their protective effect is mediated by binding to pathogens in gastrointestinal tract. Rump *et al.* (1992) demonstrated that the incidence of chronic diarrhea among HIV individuals can be significantly reduced by diet containing bovine colostrum immunoglobulin concentrate.

#### *Micronutrients and immunity*

##### *Vitamins and immunity*

Vitamins are essential constituents of our diet that have long been known to influence the immune system (Mora *et al.*, 2008). There are nine water soluble vitamins including the eight in the vitamin B complex and vitamin C. The B complex vitamins

include thiamin, riboflavin, niacin, B<sub>6</sub> (pyridoxine), B<sub>12</sub>, folic acid, biotin and pantothenic acid.

Humoral and cell mediated immunity are affected by vitamin B<sub>6</sub> deficiency and supradietary intakes. Vitamin B<sub>6</sub> is involved in lipid metabolism, nucleic acid and protein biosynthesis. It also helps to maintain normal nerve function and the formation of red blood cells (Heinz *et al.*, 2010). Vitamin B<sub>6</sub> deficiency impairs lymphocyte maturation, growth and proliferation, and antibody production; it suppresses the production of Th1 cytokines and, thus, promotes Th2 responses (Maggini *et al.*, 2007). Talbott *et al.* (1987) examined the effect of a supradietary vitamin B6 (50 mg/day) supplement in healthy elderly and noted increases in mitogen stimulated lymphocyte proliferation and helper T cells. Meydani *et al.* (1991) showed that IL-2 production and responses to T and B cell mitogens are adversely affected by low vitamin B<sub>6</sub> status in elderly and that short term supplementation with 50 mg/day increased these indices of immune function. Casciato *et al.* (1984) have reported that reduced immunocompetence of renal dialysis patients is reversed by 210-600 mg/week of pyridoxine.

Vitamin B<sub>12</sub> enhanced T cell proliferative responses to concanavalin A (Con A) and immunoglobulin synthesis of B cells by pokeweed mitogen (PWM) (Sakane *et al.*, 1982). It has been reported that vit. B<sub>12</sub> deficiency caused suppression of protective immune responses to viruses and bacteria in an animal model (Vellema *et al.*, 1996). Skacel and Chanarin (1983) observed reduction in bactericidal activity in patients with megaloblastic anemia and low serum vitamin B<sub>12</sub>. Moreover, Crist *et al.* (1980) noted neutropenia and leukopenia and related white blood cells abnormalities in children with low vitamin B<sub>12</sub>.

Individuals with low folate levels have impairments in neutrophil function that can be corrected by improved nutrient status (Youinou *et al.*, 1982). Chandra (2004) reported that the impairment in immunocompetence is noticeable as early as 35-40 years old in many individuals. A variety of nutrients are affected: zinc, iron, beta-carotene, Vitamins B<sub>6</sub>, B<sub>12</sub>, C, D and E and Folic acid. The causal interaction between nutritional deficiencies and impaired immunity has been known in children; a similar relationship has been postulated in the elderly. Biotin is a coenzyme for several enzymes that catalyze carboxylation reaction. Fischer *et al.* (1982) demonstrated that carboxylase deficiency is associated with lymphocyte mediated suppressor activity which is corrected by 10 mg/day biotin in pediatric patients.

Vitamin C deficiencies are found to be associated with decreases in the bactericidal activity and locomotion of neutrophils and macrophages and decreases in resistance to microbial infection (Chandra, 2004). Several mechanisms of ascorbate mediated immunostimulation have been proposed including: (a) modulation of intracellular cyclic nucleotide levels, (b) modulation of prostaglandin (PG) synthesis, (c) protection of 5'-lipoxygenase, (d) enhancement of cytokine production. (e) antagonism of the immunosuppressive interactions of histamine and leukocytes and, (f) neutralization of phagocyte derived autoreactive and immunosuppressive oxidants (Anderson *et al.*, 1990; Sorice *et al.*, 2014). Ziemiński *et al.* (1986) noted significant increases in serum IgG and IgM levels in elderly woman receiving 400 mg ascorbic acid /day.

The four fat soluble vitamins are A, D, E and K. normally act interactively together. β-Carotene (provitamin A) can protect phagocytic cells from autooxidative damage, enhance T and B lymphocyte proliferative responses, stimulate effector T cell functions, promote the production of cytokines and increase macrophage, cytotoxic T cell and natural killer cell tumoricidal capacity (Bendich, 1991). The role of vitamin A in resistance to infection is well established (Field *et al.*, 2002). The mechanism by which vitamin A reduces infection may be through modification of epithelial integrity and function, lymphoid mass, and specific and non specific immunity of host. Mora *et al.* (2008) demonstrated that vitamin A deficiencies have an important influence on the immune response in human. Moreover, HIV infected pregnant woman should eat food rich in vitamin A, while maternal vitamin A deficiency increases the risk of congenital HIV and AIDS (Cunningham-Rundles *et al.*, 2002). Besides, Vitamin A supplementation significantly reduces all-cause of mortality when given between 6–59 months (WHO, 2011). 1,25-dihydroxyvitamin D<sub>3</sub> has been recognized as an immunoregulatory hormone serving as immunomodulatory agent of both non specific and specific immunity (Mora *et al.*, 2008).

As vitamin D receptor is expressed on immune cells (B cells, T cells and antigen presenting cells), it has the capability of acting in an autocrine manner in a local immunologic milieu and can modulate the innate and adaptive immune responses (Aranow, 2011). Also, vitamin D plays an important role in pulmonary resistance and its deficiency has been linked to various respiratory infections (de Tena *et al.*, 2014). It affects both cytokine and immunoglobulin production. Besides it has a beneficial effects in autoimmune thyroiditis, multiple sclerosis and

rheumatoid arthritis. Vitamin D also upregulated the lipopolysaccharide receptor on the surface of T lymphocyte and suppressed the vitamin A induced expression for immunoglobulin E (Zhang *et al.*, 2012). Vitamin D<sub>3</sub> may protect against adipose tissue inflammation by disrupting the deleterious cycle of macrophage recruitment (Gao *et al.*, 2013).

Supplementation with antioxidant vitamins especially with vitamin E has been associated with an enhancement of immune function (Meydani *et al.*, 2004; Maslovea *et al.*, 2014). Megadose of vitamin E has a stimulatory effect on humoral and cell mediated immunity (Bauersachs *et al.*, 1993). Through its antioxidant function, vitamin E could decrease the production of immunosuppressive factors such as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and hydrogen peroxide by activated, macrophages the latter depresses lymphocyte proliferation (Pallast *et al.*, 1999). Pae *et al.* (2012) reported that vitamin E supplementation may modulate host defense against infectious pathogens.

#### *Minerals and immunity*

Selenium (Se) via its incorporation into cytosolic glutathione peroxidase (GSHPx) and biomembranes has been associated with the expression of specific, non specific and cell mediated immune response (Spallholz, 1990; Teixeira *et al.*, 2014). Selenium supplements augmented the cellular immune response through an increased production of IF $\gamma$  and other cytokines, T cell proliferation, and increase in T helper cells. Humoral immune responses were not affected by Se. Selenium supplemented subjects showed more rapid clearance of the poliovirus (Broome *et al.*, 2004). Se protects the cardiac muscle from invasion by pathogens. Se deficient mice were more susceptible to infections by coxsackievirus as well as influenza virus (Beck, 2001). Moreover Se decreases the possibilities of AIDS virus infection (Zagrodzki, 2004).

Zinc plays a catalytic, structural and regulatory role for enzymes, proteins and transcription factors and is thus a key trace element in immune responses. Dietary zinc supplementation has been shown to enhance immune response in elderly (Chandra, 2004). Moreover, zinc increases the secretion of IL-I and affects the humoral immune response (Salyer *et al.*, 2004). Zinc has been shown to antagonize the detrimental effects of toxic dietary metals, such as nickel, on the immune response (Schiffer *et al.*, 1991). Copper/zinc superoxide dismutase (SOD), metalloenzyme is directly involved in immunity and antioxidant defenses. In addition, thymulin a key thymic factor is zinc dependent (Goldberg, 1994).

Iron salts have been reported to enhance the immunity (Chandra, 2004). Iron in metalloenzymes or proteins participates directly in immunity such as iron catalase and lactoferrin (Ha and Zemel, 2003). Iron supplementation in population with high incidence of iron deficiency anemia has been shown to decrease the morbidity from infections and diarrheal diseases (Scrimshaw *et al.*, 1990). The action of iron occurs via influencing the innate immune responses.

Copper is an important metal in regulating the activity of certain metalloenzyme as superoxide dismutase and has an important role in immunity. Mice receiving excess copper for eight weeks demonstrated suppressed mitogen induced lymphoproliferative responses (Pocino *et al.*, 1990). In addition, T and B lymphocyte response to mitogen stimulation were impaired in subjects with copper deficiency and in subject with low copper diet (Kelley *et al.*, 1995). Moreover, copper enhances antitumor immune response in a drug resistant tumor model (Chakraborty *et al.*, 2014).

Trivalent chromium (Cr III) is an essential micromineral (trace element). It enhances immunity (Yuan *et al.*, 2014) and its addition to incubated pulmonary macrophages 10-20  $\mu\text{g/L}$  stimulates directly the cellular activity of macrophages and phagocytosis (Lee *et al.*, 2000). It also increases serum IgM, total immunoglobulin and decreases serum cortisol. Magnesium has a strong relation with the immune system, in both nonspecific and specific immune response, also it has known effect on innate and acquired immune response (Tam *et al.*, 2003).

#### *Nutraceuticals and immunity*

Probiotics are beneficial microbes that confer a realistic health benefit on the host (Hardy *et al.*, 2013). Probiotics have beneficial effects on intestinal immunity, prevention of infection, elimination of toxins and eradication of microbial pathogens (Corthésy *et al.*, 2007; Duncan and Flint, 2013). Probiotic bacteria have been reported to exert immune modulatory effects by increasing macrophage phagocytosis and increasing natural killer cell activity and numbers. Excessive production of proinflammatory cytokines may lead to chronic inflammation which increase the risk of cancer. Probiotics have the ability to modulate the immune response and counter the inflammatory process (Philpott and Ferguson, 2004). Many elderly subjects are at increased risk of infectious and noninfectious diseases due to an age related decline in lymphoid cell activity. Dietary supplementation with probiotic lactic acid bacteria (LAB) enhances natural killer cell activity and thus improves the immune system

in elderly (Gill *et al.*, 2001; Duncan and Flint, 2013).

Prebiotics are non digestible food stuffs such as fiber and oligosaccharides which enter the colon and are metabolized by probiotics (Fric, 2002). Vulevic *et al.* (2008) observed that administration of galactooligosaccharides to healthy elderly persons results in an increase in the numbers of beneficial bacteria, especially bifidobacteria, increases in phagocytosis, NK cell activity, the production of antiinflammatory cytokine interleukin-10 (IL-10) and reduction in the production of proinflammatory cytokines. Bunout *et al.* (2004) demonstrated that dietary supplement providing lactobacillus and fructooligosaccharides among other nutrients to healthy elderly vaccinated against influenza and pneumococcus increased the activity of natural killer cells and the production of IL-2.

Dietary sources of preformed purines and pyrimidines seem to be important for optimal function of the cellular immune response. Kulkarni *et al.* (1994) demonstrated that a diet free of purine or pyrimidines suppresses both in vitro and in vivo cell-mediated immune responses and that reversed by dietary nucleotide supplementation.

There is evidence of the potential role of exogenous nucleotides as regulators of the immune function. Studies have shown that dietary nucleotides stimulate the humoral immune response to T-dependent antigens and raise the total antibody level. They also improve the response to vaccines and decrease the morbidity and increase the tolerance to antigens (Maldonado *et al.*, 2001; Sacks *et al.*, 2003). Grimble (2001) showed that single nucleotide polymorphisms in the genes controlling proinflammatory cytokine production adversely influence the immune response. He added that n-3 polyunsaturated fatty acids (PUFA), glutamine, arginine, S-amino acids and nucleotides are important components of immunonutrient mixes. Nucleotides enhanced the immune response by exerting a direct effect on lymphocyte proliferation.

Cellular and humoral immunity are both impaired in patients with nucleotide deficiency. Cells treated with deoxycoformycin, an inhibitor of adenosine deaminase, don't respond to mitogen stimulation because of a block nucleotide level (Thuller *et al.*, 1985). Uracil administration can restore delayed type hypersensitivity (DTH) and T-cell response to antigens. Uracil has also been reported to reverse the immunosuppression associated with blood transfusion (Kulkarni *et al.*, 1986).

Glutathione (GSH) is the most abundant low molecular weight thiol containing compound in cells and a strong free radical scavenger. Furukawa *et al.* (1987) reported that dietary GSH supplementation in

old mice significantly enhanced DTH response and lymphocyte proliferation. Moreover, lymphocytes exposed to sulphhydryl oxidizing agents have a decreased proliferative response to mitogens. (Noelle and Lawrence, 1981). Adequate intracellular levels of GSH are necessary for lymphocyte activation. The depletion of GSH lowers the mitogenic responses and the in vitro addition of this tripeptide into culture medium reverses it.

The effect of dietary fat on immunity may be mediated, in part by, alteration in cell membrane composition, serum lipoproteins, or hormonal status (Calder and Newsholme, 1993). It's well established that essential fatty acid deficiency results in lymphoid atrophy and depressed antibody responses (Garcia *et al.*, 2014). Small dietary amounts of linoleic acid, n-6 fatty acid, act as a substrate for prostaglandin (PG) and leukotriene (LT) synthesis, are required for the normal propagation and maturation of cell mediated immune response. High intakes of n-6 polyunsaturated fatty acids (n-6 PUFA) such as linoleic and/or arachidonic acid, increase synthesis of PGE<sub>2</sub> by macrophage, suppress DTH and lymphocyte proliferation. This immunosuppression associated with fatty acids might be beneficial in conditions involving an overactive immune response such as rheumatoid arthritis (Gallin *et al.*, 1988). However in healthy elders a diet rich in n-6 PUFA produced reduction in the activity of NK cells. Therefore, from an immunological point of view, a high intake of n-6 PUFA may be inadvisable (Rasmussen *et al.*, 1994).

Endres *et al.* (1989) reported that fish oil supplementation in healthy adults suppressed the synthesis of the proinflammatory mediators IL-1 and TNF. These actions are consistent with the decreased inflammatory responses in patients receiving n-3 PUFA and with the lower incidence of inflammatory diseases such as asthma and type I diabetes in population. Also, administration of increasing doses of n-3 fatty acids improves cell mediated immune function (Alexander *et al.*, 1986). However there is a balance between the immunostimulatory, anti-inflammatory, and immunosuppressive actions of n-3 supplementation (Meydani *et al.*, 1991)

Arginine, an amino acid, that improves the immune parameters during physiological stresses (Liu *et al.*, 2014). Dietary arginine has also been reported to be important for the maintenance of NK cell activity (Lieberman *et al.*, 1992). Some evidence suggests that arginine is associated with reduced length of hospital stay after cancer surgery (Shor *et al.*, 2004). Immune enhancing diets that have arginine were beneficial in moderate to severely malnourished patients undergoing gastrointestinal

surgery and traumatic patients (Sacks *et al.*, 2003; Chermesh and Shamir, 2004).

Glutamine is the most abundant plasma free amino acid and functions in a wide variety of metabolic reactions. These include its provision as a fuel to lymphocytes and mucosal cells of the gastrointestinal tract. It has been identified as a critical nutrient for maintenance of the intestinal immune system and secretory IgA synthesis. It is also essential for the prevention of bacterial translocation from the gut, following stress of burns, surgery or trauma (Alverdy, 1990). Grimble (2001) demonstrated that glutamine improves the immune response either by direct effect on lymphocyte proliferation or by acting indirectly on the antioxidant status. Mager and Sloan, (2003) demonstrated that amino acids and peptides contribute to the innate lung defense. In agreement with them, Grimm and Kraus (2003) proved that glutamine, taurine, cysteine and arginine enhance the immune response in critically ill patients. Glutamine utilization may provide optimal conditions for the synthesis of purine and pyrimidine nucleotides during the cell cycle. Any decrease in the availability of glutamine to lymphocyte decreases their rate of proliferation and their ability for rapid response to immune challenges (Heyland *et al.*, 2001).

#### *Nutrient-nutrient interactions and the effect on immunity*

Availability of one nutrient may impair or enhance the action of another in the immune system, as reported for nutrients such as vitamin E and selenium, vitamin E and vitamin A, zinc and copper, and dietary fatty acids and vitamin A. Nutrient-nutrient interactions may negatively affect the immune function such as the effect of excess calcium which interferes with leukocyte function by displacing magnesium, thereby reducing cell adhesion (Kubena and McMurray, 1996).

Vitamin E and selenium both together protect the unsaturated membrane phospholipids and protein sulfhydryl groups from oxidants that may impair cellular function. Humoral immunity was improved in rats given selenium and vitamin E compared with rats deficient in both nutrients. A pronounced effect occurred on immunoglobulin M (Bauersachs *et al.*, 1993).

A synergistic effect with supplementation of vitamin E and C on inhibition of release of arachidonic acid was observed. Because inhibition of arachidonic acid has been reported to result in stimulation of immune cell responses and suppression of tumor growth. El Attar and Lin (1992) suggested supplementation of both vitamins to cancer patients.

An antagonistic effect between vitamin E and A has been noted. This effect may occur because of the suppression of gastrointestinal absorption and of tissue reserves of vitamin E by high levels of vitamin A (Eicher *et al.*, 1994). However, the bactericidal activity of neutrophils was suppressed by supplementation of either nutrient, whereas supplements of both enhanced neutrophil activity.

Vitamins A and D are known to have a hormone like effects on the maturation and differentiation of monocytes. There is an apparent antagonism between both vitamins. Vitamin A increases the production of eicosanoids. The addition of vitamin D and vitamin A did not induce additional product of arachidonic acid cascade (Sellmayer *et al.*, 1994). By contrast, another study has reported that retinoic acid and vitamin D act synergistically to induce macrophage like properties in some monocytic cells (Tiami *et al.*, 1991).

Jackson *et al.* (1994) found that calcium, magnesium, and manganese were needed for normal function of leukocytes, but excess calcium ions displaced magnesium, thus reducing the adhesion of cells. Copper deficiency resulted in significant reductions in phagocytosis which can be reversed by iron (Niederman *et al.*, 1994). Supplementation of chromium alone significantly increased the lymphocyte proliferation and subsequently the stimulation index, the combination of chromium and copper supplementation failed to increase the index. Thus, the presence of copper prevented the enhancing effect of chromium on lymphocyte proliferation.

The combined supplementation of zinc and vitamin A in children normalized conjunctival epithelium in a synergistic manner and significantly increased the proliferative response of lymphocytes (Kramer *et al.*, 1993; Li and Li, 2007).

Immunosuppression associated with polyunsaturated fatty acids was reversed by adding vitamin E. Alterations in macrophages from rats fed a diet rich in PUFA were antagonized by vitamin E addition. Similarly, PUFA inhibition of lymphocyte proliferation *in vitro* was improved by addition of vitamin E. The suppression might be attributable to oxidative products from fatty acids which was removed by the antioxidant action of vitamin E (Calder and Newsholme, 1993). Moreover, the suppressed response of T-lymphocytes to mitogens that occurred when n-3 PUFA were fed to human beings was normalized by increased intakes of vitamin E (Kramer *et al.*, 1991).

Vitamin A deficiency alone enhanced tumor burden, whereas fatty acid deficiency alone protected against tumor formation. In rats consuming the diet deficient in both vitamin A and fat, the fatty acid

deficiency protected the rats against tumor burden expected to be induced by vitamin A deficiency (Khanduja *et al.*, 1994).

## Conclusion

Effective nutritional interventions in the immune system may find value not only in therapeutic applications, but also in the prophylactic treatment of subjects at risk of immunoincompetence because of illness or prior to immunosuppressive drugs and surgical regimens.

Thus dietitians should encourage the intake of a variety of nutrients to promote proper balance among all nutrients. For consumers who are not deficient in one or more nutrients but nevertheless are intent on using supplements, products that provide multiple nutrients such as multivitamin and multimineral without supplying excess amounts should be encouraged. Some nutraceuticals are beneficial for the immune system. Far more research into nutrient-nutrient interactions and immune function particularly in human subjects is needed. At this time, the best dietary advice to enhance immune function in healthy people is to ensure variety, balance and moderation of the nutrients.

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