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ORIGINAL COMMUNICATION

Changes in the immune system are conditioned by nutrition

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Undernutrition due to insufficient intake of energy and macronutrients and/or due to deficiencies in specific micronutrients impairs the immune system, suppressing immune functions that are fundamental to host protection. The most consistent abnormalities are seen in cell-mediated immunity, complement system, phagocyte function, cytokine production, mucosal secretory antibody response, and antibody affinity. There is a number of physiological situations such as ageing and performance of intense physical exercise associated with an impairment of some immune parameters' response. Nutrition can influence the extent of immune alteration in both of them. There are also numerous pathological situations in which nutrition plays a role as a primary or secondary determinant of some underlying immunological impairments. This includes obesity, eating disorders (anorexia nervosa and bulimia nervosa), food hypersensitivity and gastrointestinal disorders as some examples. The implications of nutrition on immune function in these disorders are briefly reviewed.
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Introduction

The immune system acts to protect the host from infectious agents that exist in the environment (bacteria, viruses, fungi, parasites) and from other noxious insults. To this end, it relies on two functional branches: the innate and the acquired, both involving a diversity of blood-borne factors (complement, antibodies, and cytokines) and cells (macrophages, polymorphonuclear cells, and lymphocytes). The adequate functioning of this defensive system is critically determined by nutrition, and, as a consequence, so is the risk of illness. In this sense, undernutrition due to insufficient intake of energy and macronutrients and/or due to deficiencies in specific micronutrients impairs the immune system, suppressing immune functions that are fundamental to host protection. These changes are associated with an increased risk of infections, which, in turn, produce physiological changes that worsen nutritional status (Chandra & Newberne, 1977; Chandra, 2002).

Based on this close relationship between nutrition and immunity, for at least the last two decades, immunocompetence assays are being used as sensitive functional indices in the assessment of the nutritional status.

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Effects of nutrients on the immune system

Without adequate nutrition, the immune system is clearly deprived of the components needed to generate an effective immune response. Human malnutrition is usually a complex syndrome of multiple nutrient deficiencies. However, observations in laboratory animals deprived of one dietary element, as well as findings in those rare patients with a single nutrient deficiency, have confirmed the crucial role of several vitamins, minerals and trace elements in the maintenance of immunocompetence. This includes vitamin A, beta-carotene, folic acid, vitamin B_6, vitamin B_{12}, vitamin C, vitamin E, riboflavin, iron, zinc, and selenium (Grimble, 1997; Chandra, 2002). Antioxidant nutrients, for example, play a pivotal role in maintaining the antioxidant/oxidant balance in immune cells and in protecting them from oxidative stress and preserving their adequate function

(Victor & de la Fuente, 2002). The addition of the deficient nutrient back to the diet can restore immune function and resistance to infection. However, excessive amounts of some nutrients also impair immune function (Calder and Kew, 2002).

As crucial components in the diets, lipids are substances that exert a profound effect in the modulation of the immune system. The fatty acid composition of lymphocytes, and other immune cells, is altered according to the fatty acid composition of the diet. Therefore, an immunomodulatory role has been suggested for dietary lipids, which could be used in the management of some diseases involving inflammation processes, such as autoimmune diseases (De Pablo & Alvarez de Cienfuegos, 2000).

Relationship between physiological and pathological situations conditioned by nutrition and the immune system

Protein energy malnutrition

Nutritional deprivation, such as protein energy malnutrition (PEM), often causes immunodeficiency leading to increased frequency and severity of infection, thymus atrophy and wasting of peripheral lymphoid tissue (Chandra & Kumari, 1994), with the subsequent impairment of immune responses, especially in the cell-mediated mechanisms. Malnutrition, independent of its origin (protein, mineral, or vitamin deficient supply), consistently results in changes in the thymus gland. The organ undergoes a severe atrophy due to apoptosis-induced thymocyte depletion plus decreased thymocyte proliferation (Chandra, 1992). Also, a decrease in thymic hormone production has been repeatedly documented in various types of nutrient deprivation. Recently, a hypothesis has been put forward that hormonal control of malnutrition-induced thymocyte depletion could exist: involving a decrease of leptin and a consequent rise of serum glucocorticoid hormone levels (Savino, 2002).

Ageing

Older individuals tend to have a high prevalence of nutrient deficiency. Although very often the manifestations of these deficiencies are only subclinical, the effects upon the immune system and cognitive function are remarkable. The clinical outcome of impaired immunity is an increased incidence of common infections affecting the upper and lower respiratory, urinary, and genital tracts. According to human studies, changes in immunity associated with ageing include decreased delayed-type hypersensitivity (DTH) responses, reduced IL-2 production and proliferation of lymphocytes, reduction in serum IgA and decreased antibody titre after vaccination (Chandra, 2002). The number of circulating T lymphocytes is slightly decreased. The ratio mature/immature T lymphocyte decreases, as does the ratio naïve/memory T cells, and NK cells are more numerous (Lesourd & Mazari, 1999). However, those functions that are more related to oxidative stress such as adherence, free radical and proinflammatory cytokine production increase with age (Victor & De la Fuente, 2002). These mechanisms are associated with the general decline of the immune system activity. Nutrient supplements, such as vitamin B_6, zinc, vitamin C, vitamin E may be important for health promotion and prevention of certain diseases. However, the optimum doses for antioxidant supplementation are still not clear, since in certain cases potential deleterious effects of oversupplementation have emerged from some clinical trials.

Obesity

Limited and often controversial information exists comparing immunocompetence in obese and nonobese subjects as well as the cellular and molecular mechanisms involved. The mechanisms responsible for increased risk of infection and poor antibody response among obese subjects are unknown, but may be linked to the negative effect that their metabolic milieu produces on immunity (Lamas *et al*, 2002). In this sense, much evidence supports a link between adipose tissue metabolism and immunocompetent cell functions. This includes the closely related factors leptin and tumour necrosis factor-alpha (TNF-α) in adipose tissue.

Different animal models of obesity have shown a decrease in all T-lymphocyte subsets and the B-cell population (Kimura *et al*, 1998), and also lymphocyte responsiveness to different mitogens is lower in obese animals compared to lean ones (Tanaka *et al*, 1998). As occurs in animal models, most investigations in humans confirm a lower capacity of lymphocytes to proliferate in response to mitogen activation. However, different and even opposite results have been found regarding leukocyte and lymphocyte subset counts, probably due to heterogeneity in the subjects studied. Moreover, those studies assessing the immune response in obese patients after weight loss or nutritional deprivation have also produced variable results.

Eating disorders

Studies on the impact of eating disorders, such as anorexia nervosa (AN) or bulimia nervosa (BN), over the immune system, have produced controversial findings. On the one hand, patients with AN frequently show a tendency to leukopenia together with relative lymphocytosis (Marcos *et al*, 1993) and a decreased delayed-type hypersensitivity skin test response (Varela *et al*, 1988). But, on the other hand, immune impairments are less severe than would be expected considering the highly defective nutritional status of the patients, and also, they seem to be surprisingly free of infectious complications or even common viral infections (Marcos, 2000). To understand why these patients are less prone to infection than subjects with typical malnutrition, there are several points that are worth noting. Firstly, while in starvation the diet is deficient in multiple vitamins and proteins, in AN the primary dietary inadequacy is of

carbohydrates and fats. Also, hypothetically, some of the complex interactions occurring between cytokines and the endocrine system and the central nervous system could provide some compensatory mechanisms to adapt to the limited nutrient supply and possibly result in the perceived lack of infection symptoms. A dysregulated cytokine production and the altered acute-phase response to infection, as well as cortisol and leptin, are considered to be potential factors involved in the adaptation processes occurring in these syndromes (Nova *et al*, 2002).

Physical exercise practice

The effect of exercise on immune response is multifaceted, depending upon the type of exercise and the intensity of effort relative to the individual's state of training. In general, it is accepted that while moderate exercise enhances immune functions, high-intensity physical activity and periods of heavy training can suppress various immune response parameters. Considerable evidence indicates that improper nutrition and psychological stress increase the negative effect of heavy exertion upon the immune system. Some sportswomen performing sports that emphasize leanness, as well as weight-classification sports, suffer from these three conditions, namely, heavy training, inadequate nutrition and competition-related stress. Under this situation, their immune system has been proved to be affected, even before their daily routine of exercise. Basal leukocyte, lymphocyte, and T lymphocyte subset counts from elite female gymnasts going through long hours of daily training, have been shown to be lower than those of healthy sedentary age-matched controls (López-Varela *et al*, 2000). Differences have also been found in cytokine production by *in vitro* stimulated blood mononuclear cells from female gymnasts in comparison with controls (Nova *et al*, 2001).

Immunocompetence, then, can be used as an index of the seriously compromised nutritional status of some athletes. In fact, there are some similarities between gymnasts and patients with eating disorders in their immune abnormalities that could be explained by some factors shared in common such as their restrictive dietary habits, continuous activity, hormone alterations, and the stressful environment.

Food hypersensitivity

Diet during gestation and early childhood has a profound effect on many physiological functions and on the occurrence of several disorders. In this sense, it is known that prolonged breast feeding, the use of a partially hydrolysed formula, and delayed introduction of certain 'allergenic foods' are associated with reduced occurrence of food hypersensitivity. This is an adverse reaction to dietary components with an immunologic mechanism that contributes to the development of eczema, gastroenteropathology, asthma, and hay fever. The preventive measures mentioned are especially advisable for those children at higher risk according to family history. Consequently, breastfeeding should be promoted for other reasons as well. It reduces the risk of necrotizing enterocolitis, diabetes mellitus type I and type II, lymphoma, and infections in general throughout life (Chandra, 2000).

Gastrointestinal disorders

The primary activity of mucosal immune response is to protect the mucosa by blocking microbial, toxin and antigen entry through secretion and transport of IgA to the lumen of the gut, a process mediated by a special type of memory T cell capable of providing B cell help. These type of cells can be found in the lamina propia of the intestinal barrier and can therefore interact and receive signals from endogenous

Table 1 Brief presentation of some physiological and pathological situations in which nutrition acts as a primary or a secondary determinant of immune function impairment

Physio/pathological situation	*Some observed effects on immunity*	*Nutritional advise*
PEM	Thymus atrophy, leukopenia, ↓ CD4/CD8	Reversible with refeeding
Ageing	↑ frequency of infections, ↓ IL-2 production, ↓ lymphocyte proliferation	Beneficial nutrient supplementation
Obesity	Immunosuppression, ↑ frequency of infections, poor antibody response	Rationally controlled weight loss and then weight stability
Eating disorders	Leukopenia, relative lymphocytosis, ↓ DTH response, altered pattern of cytokine secretion	Nutritional rehabilitation Nutritional education and correction of dietary habits
Sports requiring low body weight	Leukopenia, lymphopenia, ↓ DTH response, altered pattern of cytokine secretion.	Nutritional rehabilitation Nutritional education and correction of dietary habits
Food allergy	Hyper-response of immunologic mechanisms leading to asthma, atopic eczema and other allergic manifestations.	Strict avoidance of allergenic food. Prevention through breast feeding, hydrolysed milk formulas and delayed introduction of allergenic foods
Gastrointestinal disorders	Those secondary to nutrient deficiencies Failure of mucosal mechanisms of defence (altered IgA-mediated protection) Impairment of the homeostatic response to limit epithelial inflammation	Administration of probiotics with adequate bacteria strains

microbiota of the gut. Commensal bacteria may exert a dual function: the stimulation of mucosal mechanisms of defence on one side (for instance, by lactobacilli) and the maintenance of homeostasis of the immune response on the other (Schiffrin & Blum, 2002). Reduction of normal commensal bacteria in the context of infection or after antibiotic treatment may interfere with nutrient availability and impair beneficial stimulation of gastrointestinal immune response. In this sense, probiotics have proved helpful in prevention of infectious diarrhoea and shortening of the episodes. On the other hand, an impairment of the homeostatic control by immunomodulatory cytokines, normally working to downregulate or limit the extent of an initial proinflammatory event triggered by nonpathogenic bacteria, may underlay the development of inflammatory bowel disease. Thus, the manipulation of the host microflora to influence underlying immune responses may represent a new possibility in the prevention or management of gastrointestinal pathophysiological disorders.

There are more pathological situations with a clear participation of immune mechanisms that can be modulated or conditioned by food components and nutrients. This includes cancer, inflammation processes such as atherosclerosis, rheumatoid arthritis, bronchial asthma, cystic fibrosis, fibromyalgia; but further studies are needed to elucidate the underlying mechanisms and how to perform adequate nutritional intervention. Overall, the exploration of functional foods seems clearly interesting in the context of a Western civilization facing up to a progressive increase in immune-mediated and gut-related health problems.

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