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Symposium on 'Nutrition, infection and immunity'

Nutrition and immunology: from the clinic to cellular biology and back again*

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Diet and immunity have been known to be linked to each other for centuries. In the last 30 years systematic studies have confirmed that nutrient deficiencies impair immune response and lead to frequent severe infections resulting in increased mortality, especially in children. Protein–energy malnutrition results in reduced number and functions of T-cells, phagocytic cells and secretory immunoglobulin A antibody response. In addition, levels of many complement components are reduced. Similar findings have been reported for moderate deficiencies of individual nutrients such as trace minerals and vitamins, particularly Zn, Fe, Se, vitamins A, B_6, C and E. For example, Zn deficiency is associated with profound impairment of cell-mediated immunity such as lymphocyte stimulation response, decreased CD4+:CD8+ cells, and decreased chemotaxis of phagocytes. In addition, the level of thymulin, which is a Zn-dependent hormone, is markedly decreased. The use of nutrient supplements, singly or in combination, stimulates immune response and may result in fewer infections, particularly in the elderly, low-birth-weight infants and malnourished critically-ill patients in hospitals. The interactions between nutrition and the immune system are of clinical, practical and public health importance.

Trace elements: Ageing: Low-birth-weight infants: Immune responses: Infection

Nutrition and risk of infection

The causal relationship between the conjugal pair of famine and pestilence has been known for millennia. It is recognized that malnutrition and infection are two major obstacles for health, development and survival worldwide, and that poverty and ignorance are the most significant contributing factors. Epidemiological observations have confirmed that infection and malnutrition aggravate each other. However, nutrition does not influence all infections equally. For some infections (e.g. pneumonia, bacterial and viral diarrhoea, measles and tuberculosis) there is overwhelming evidence that the clinical outcome is affected adversely by nutritional deficiency. For other infections (e.g. viral encephalitis and tetanus) the effect of nutritional status is minimal. For still other infections (e.g. influenza virus and human immunodeficiency virus) nutrition exerts a moderate influence.

There are many causes of increased susceptibility to infection among underprivileged malnourished communities, and I shall focus on impaired immunity as an important contributing factor.

Nutritional status and immune response

It has now been established that nutritional deficiency is commonly associated with impaired immune responses, particularly cell-mediated immunity, phagocyte function, cytokine production, secretory antibody response, antibody affinity and the complement system. In fact, malnutrition is the commonest cause of immunodeficiency worldwide.

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In addition to protein–energy malnutrition, deficiencies of trace elements, vitamins and essential fatty acids impair immunity. Zn is a prime example of a micronutrient that is essential for optimum immune responses. In Zn deficiency there is reduced lymphocyte proliferation response, decreased antibody production after challenge with T-dependent and alloantigens, lower CD4+:CD8+ cells and helper function, impaired natural killer cell activity and reduced thymulin activity. In addition, phagocyte function is impaired, both ingestion and chemotactic migration. Zn is a cofactor for phospholipases A_1 (*EC* 3.1.1.32) and C and its deficiency decreases NADPH oxidase activity.

Detailed discussion can be found in original publications cited in selected review articles listed in the Bibliography to this paper.

Applied significance

Nutritional regulation of immunity and risk of illness have several practical applications. First, changes in immune response occur early in the course of nutritional deficiency. Thus, we can employ immunocompetence as a sensitive functional indicator of nutritional status. In patients with obvious primary or secondary malnutrition, the number of T lymphocytes is a useful measure of response to supplementation therapy. Second, anergy and other immunological changes correlate with poor outcome both in medical and surgical patients in terms of complications, duration of hospital stay and mortality. This correlation is particularly useful when impaired immunity is considered in association with hypoalbuminaemia. In field surveys impaired cell-mediated immunity and reduced concentrations of complement precede and predict the occurrence of infection. Third, opportunistic infections occur more frequently among patients with cancer who are also malnourished. The incidence of complicating infections can be reduced if appropriate preventative and therapeutic nutritional management is carried out in patients with leukaemia. Fourth, there is an uncanny similarity between the immunological findings in nutritional deficiencies and those seen in acquired immune deficiency syndrome. It has been postulated that nutritional deficiency may influence the biological gradient and natural history of this infection. Fifth, response to immunization is modulated by the nutritional status of the host, and protective efficacy of vaccines may be suboptimal in undernourished individuals. Sixth, immune response can be used to define safe and lower limits of nutrient intake.

Our knowledge of nutrition–immunity interactions has opened up exciting possibilities for nutritional intervention for both primary and secondary prevention of infection in high-risk groups. Nutritional deficiencies are seen often in hospitalized patients. These individuals are susceptible to developing life-threatening opportunistic infections. Recent work with animals has highlighted the value of nutrient-enriched diets in improving immune responses and survival following challenge with organisms such as *Listeria*, and limited clinical studies have confirmed these observations. Similarly, a large proportion of the elderly have reduced dietary intakes and low blood levels of various nutrients. They are also prone to respiratory infection. Several investigations have shown a correlation between nutritional status and incidence of infection in old age. The results of a few intervention trials indicate that modest supplements of micronutrients improve immune responses and, more significantly, reduce the incidence of respiratory infection and antibiotic usage. In addition, post-vaccination immune responses are higher in malnourished subjects given nutritional supplements than in unsupplemented controls.

Interactions between nutrition and immunity in the elderly serve as an important model for both fundamental and clinical applications. This topic has been reviewed recently (Chandra, 1997*a*). Aging is associated with a reduction in many immune responses in most, but not all, elderly individuals. Changes in immunity associated with aging include decreased delayed hypersensitivity, reduced interleukin-2 production, decreased lymphocyte response to mitogens and antigens, a low rate of seroconversion, and decreased antibody titre after vaccination. However, in some elderly subjects the immune system is as vigorous as it was when they were young. Immune dysfunction, as assessed by the prevalence of autoantibodies, also increases in the elderly.

Some nutrients, for example vitamins B_6 and E, have been shown to have important effects on laboratory and health indicators of the elderly. However, epidemiological studies have not indicated a significant association between mortality in the elderly and vitamin E intake.

Since deficiencies of more than one micronutrient have been detected in the elderly, and since there are interesting interactions among micronutrients, several studies have examined the effect of combinations of vitamins and trace elements on immune response and incidence of infection. There is increased delayed hypersensitivity in those subjects with high retinal levels, and reduced occurrences of infection in those subjects with high levels of tocopherols. It was observed that the daily consumption of a multivitamin–mineral supplement for 1 year was associated with enhanced delayed hypersensitivity and lymphocyte response to mitogens, but these effects were reduced by ingestion of an additional 15 mg Zn daily, and further reduced by 100 mg Zn daily. Elderly hospitalized patients given a supplement of vitamins A, C and E for 4 weeks showed a high number of CD4+ and CD8+ T-cells and increased lymphocyte proliferation response to mitogen compared with the placebo group. The administration of a low-dose multi-micronutrient supplement with increased amounts of vitamin C, vitamin E and β-carotene was associated with an increase in the number of T-cell subsets, enhanced lymphocyte response to mitogen, increased interleukin-2 production, greater natural killer cell activity and increased response to influenza virus vaccine compared with the group given a placebo. In addition, supplemented subjects experienced fewer days of infection than individuals in the placebo group.

Deficiencies of vitamins and trace elements are observed in almost one-third of all elderly subjects. It is expensive and impractical to estimate dietary intake or blood levels of various nutrients in individuals. Since there is no evidence to suggest that physiological amounts of vitamins and trace elements given for prolonged periods have any toxic or adverse consequences, and given the high prevalence of

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deficiencies of several micronutients in old age, it would be prudent to opt for a suitable micronutrient supplement in modest amounts for all elderly individuals in order to achieve the maximum physiological and health benefit with the least risk of toxicity. There is ample clinical evidence that neonates have suboptimal immune response and are susceptible to infection. When growth retardation and nutritional deficiency complicate the picture, as in low-birth-weight infants, impairment of immunocompetence is more marked and longer lasting, low birth weight is associated with a higher morbidity and mortality. Infection is one of the recognized causes of increased illness in small-for-gestational age infants. In our experience, upper- and lower-respiratory-tract infections are three times more frequent in small-for-gestational age infants than in average-for-gestational age infants. Zn supplements are associated with enhanced immune responses in low-birth-weight infants, both average-for-gestational age and small-for-gestational age.

Finally, selected supplementation with one or more nutrients has been successful in reducing illness and decreasing deaths. Both vitamin A and Zn supplements in impoverished populations are associated with a decreased incidence of diarrhoea and respiratory illness in young children.

These observations have profound clinical and public health implications. The era of nutritional manipulation of the immune system has finally dawned and it brings the promise of using diet and nutrition as innovative powerful tools to reduce illness and death caused by infection.

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