Leading Article

Nutrition, immunity and infections in children

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Human health and well-being depends upon an interaction between genetic endowment or constitution on the one hand and environmental factors like nutrition, ecology (environmental sanitation, safe drinking water, pollutants, toxins etc) and life style (physical exercise, mental poise, peace, positive thinking, art of living, spirituality etc) on the other. Good nutrition and sound health go hand-in-hand. It has been known since the time of Hippocrates, that a person with good nutrition is able to ward off infections much more effectively than a person who is "fragile and weak". During most of the 20th century, the focus of research in nutrition was how to improve intake of total calories and protein in children. Therefore, the florid cases of kwashiorkor, severe protein-energy malnutrition and severe deficiencies of single micronutrients like scurvy, beriberi, pellagra and keratomalacia have significantly declined or disappeared. However, there is still widespread prevalence of diseases of public health relevance due to deficiencies of single micronutrients like iron deficiency anaemia, goitre and other iodine-deficiency disorders and milder forms of vitamin A deficiency[1]. But, of late, there has been an increasing awareness that subclinical or biochemical deficiency of certain micronutrients ("hidden hunger") is widely prevalent in developing countries which is adversely affecting the quality of human life and leading to frequent occurrence of common day-to-day gastrointestinal and respiratory infections[2]. It has been documented in developing countries that impaired immunocompetence due to nutritional deficiencies precedes overt infections and may even occur before growth failure is evident.

Nutritional status of children

Nutritional disorders are common in children due to their higher nutritional requirements to meet the demands of their physical and mental growth and because of their dependence on parents and caretakers to look after their needs. According to National Nutrition Bureau of India, 80-90% children take less than 30% PDA of green leafy vegetables. Therefore, iron consumption is inadequate in 90% of individuals in India[3]. The dietary surveys have shown that two-third of adolescents consume less than 70% PDA of vitamin A and riboflavin. Intake of calcium, vitamin B complex and vitamin C is also inadequate. Due to widespread inadequacy of dietary intakes, subclinical deficiencies of vitamin A, vitamins B_2, B_6, folate and vitamin C are seen in over 50% of apparently healthy children[4]. According to United Nations Subcommittee on Nutrition, it is difficult to meet 100% PDA of micronutrients in infants and children through home-based foods.

The immune system

A number of mechanisms protect the human host from entry of microorganisms and development of clinical infection. Host resistance can be divided into two main categories i.e. non-specific and antigen-specific (Table 1). The integrity of innate forces or frontline defences depends upon genetic or constitutional factors. They act as the first line of protection by preventing entry of microorganisms from skin and mucous membranes. The antigen-specific mechanisms of protection are adaptive or acquired by prior exposure to microorganisms or their antigenic determinants. The non-specific and antigen-specific defences support and complement each other to mount a concerted fight against invading pathogens.

Interactions between nutritional status and infections

Nutrient deficiencies have been demonstrated to have adverse effects on many immune functions[2,5,6,7] Children with malnutrition and overt or covert deficiencies of micronutrients are more vulnerable to develop a variety of common day-to-day infections. Infective illnesses are recognised to aggravate nutritional deficiencies by causing anorexia, tissue catabolism, enhanced utilization and increased losses of micro-nutrients. Acute infections thus adversely

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affect nutritional status which makes an individual more vulnerable to contract infection, thus setting-up a vicious cycle of undernutrition and recurrent infections (Figure 1). During antigen-antibody fight, there is increased production of reactive oxygen-free radicals which may further adversely affect the integrity of immune cells by damaging their mitochondria.

Table 1
Defence mechanisms of the body

Frontline non-specific innate protection	*Antigen-specific acquired protection*
• Intact skin and mucous membranes	• Cell-mediated immunity (T-cell system)
• Phagocytic cells	• Immunoglobulins (B-cell system) IgA, IgG, IgM, IgD, IgE
• Mucus	
• Cilia	
• Complement system	
• Lysozyme	
• Humoral factors	

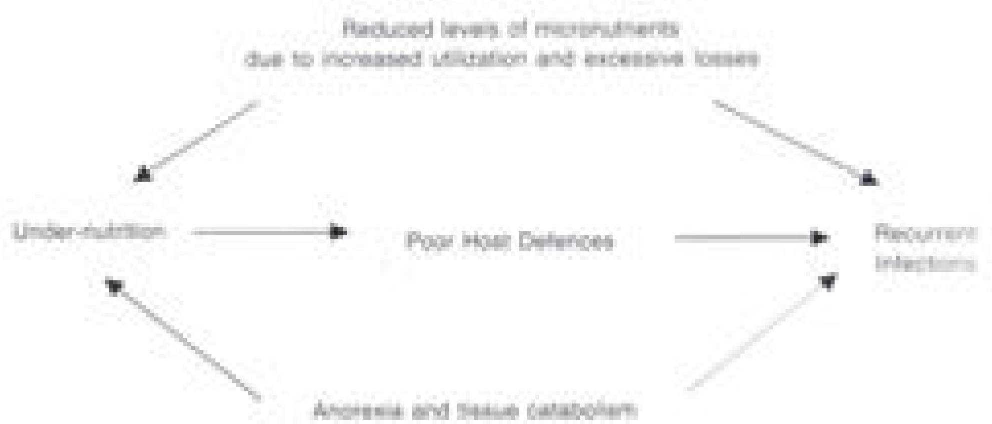

Figure 1. *Vicious cycle of undernutrition and recurrent infections*

Metabolic interactions between micronutrients

A number of metabolic interactions between various micronutrients have been identified which have great clinical relevance. Ascorbic acid is known to enhance the absorption of iron. Riboflavin has an important role in the absorption, metabolism and utilization of iron[8]. Vitamin A is required for utilization of iron for haemoglobin synthesis as it mobilizes the iron stores from liver and spleen. There is evidence to suggest that high intake of zinc may interfere with absorption of iron and copper. In fact, excessive intake of zinc (>50 mg/d) is recommended to reduce copper load in Wilson's disease. Zinc deficiency may aggravate hypovitaminosis A because zinc is required for transport of hepatic vitamin A to the target tissues[9]. Vitamin E has a sparing effect on vitamin A and ascorbic acid by protecting them from oxidation. Selenium deficiency may impair utilization of iodine because it is a key component of the enzyme which is required to convert thyroxine to triiodothyroxine. Molybdenum intake may aggravate copper deficiency because it promotes urinary excretion of copper. Magnesium helps in the absorption of calcium while calcium intake promotes absorption of vitamin B_{12} from the ileum. Therefore, these and several other metabolic interactions should be kept in mind while giving a "cocktail" of various micronutrients in clinical practice.

Nutrition and Host Defences

Research studies during the past two decades have demonstrated the importance of optimal nutrition for the functional integrity of the immune system. Both undernutrition and over-nutrition as well as deficiencies and excess of single nutrients have been shown to have adverse effects on the immune system. Recently, studies have shown that immunological dysfunction is the earliest marker of deficiency of micronutrients. Every few days our body replaces one-quarter of our immune cells. For example, neutrophils have a half-life of merely 36 hours! Therefore, the immune system needs continuous supply of vitamins and minerals for their regeneration.

Protein-calorie malnutrition

The immunologic manifestations of protein-calorie malnutrition are broad based and include atrophy of lymphoid tissue, decrease in number of lymphocytes with markedly reduced cellular and humoral immune responses[5]. It is well known that some viruses that cause only a mild illness in well-nourished children can be fatal in those with malnutrition. Arginine and glutamate are two key semi-essential amino acids which have been shown to have salutary effect on the immune system. Arginine sustains the integrity of thymus by enhancing production of thymic hormones and proliferation of thymocytes. It is credited to increase the cytotoxicity of macrophages, natural killer cells (NK cells), cytotoxic T-cells and neutrophils by releasing growth hormone, which has widespread receptors in the immune system. During arginine metabolism, nitric oxide (NO) is released which has tumoricidal and microbicidal activities, causes dilatation of blood vessels and promotes adhesion of leucocyte-endothelial cells. Glutamine is an essential nutrient for the growth and proliferation of lymphocytes and macrophages. Nucleotides, preformed purines and pyrimidines in the diet, potentiate a variety of cell-mediated immune responses.

Obesity

The immune system works most efficiently when nutritional status is optimal i.e. there is neither a deficiency nor excess of any nutrient. There is increasing incidence of obesity in children belonging to affluent societies because of unsatisfactory dietary life styles. Animal studies have shown that high energy intake impairs lymphocyte responsiveness while high fat intake suppresses T-cell functions and activity of NK cells. Fatty acids have an important role in the functioning of immune system because they are structural components of cell membranes[7]. In general, diets rich in n-3 poly-unsaturated fatty acids (PUFAs) tend to inhibit immune response, whereas those rich in n-6 PUFAs tend to promote immune response by increasing inflammation. Adequate intake of n-3 PUFAs (fish oil) has been shown to reduce the symptoms of autoimmune and inflammatory diseases. It is believed that the ratio of n-6 to n-3 PUFAs is more important than the absolute amount of these classes of fatty acids in the diet to ensure optimal nutrition and health.

Micronutrients

In the last decade, there has been a growing awareness that deficiencies of vitamins and minerals can cause reduced immune functions even when the calories and protein in the diet meet recommended intake levels[2]. Micronutrients are essential cofactors for various catalytic, structural and regulatory metabolic activities of cells. They are required for energy production, synthesis of RNA and DNA and for providing protection against reactive oxygen-free radicals. Table 2 summarizes the immuno-protective role of micronutrients on various components of immune system.

Clinical implications

There is enough clinical and research evidence that deficiency of micronutrients is associated with increased incidence and severity of common day-to-day gastro-intestinal and respiratory infections[5]. Nutritional supplements have been given to improve the immunologic status of children, reduce the incidence of infections and improve the outcome of those who get infected. There are conflicting reports regarding utility of large doses of vitamin A in preschool children in developing countries[10,11]. Some reports have documented reduction in mortality in children by 20-30% while others have not found any significant benefits. There is some evidence that supplements of vitamin A may reduce the incidence of recurrent or protracted diarrhea and respiratory infections. The intervention studies have shown that high doses of vitamin A are useful to improve the survival of children with post measles bronchopneumonia[12]. However, excessive intake of vitamin A has been shown to adversely affect the immune responses and there is potential risk of toxicity due to massive doses of vitamin A. There are conflicting reports that supplements of high-doses of vitamin C may reduce the incidence and severity of upper respiratory tract infections.

Table 2
Effects of various micronutrients on immune functions

Micronutrients	"Frontline" mucosal defences	Cell-mediated immunity	Antibody production	Cytokine patterns
Vitamins				
Vitamin A	Improved integrity	↑ DTH* ↑ NK cell** activity	Increased	↑ IL-2***
Vitamin E	—	↑ DTH ↑ immune cell proliferation	Increased	↑ IL-2 ↓ PGE_2
Vitamin C	Improved integrity	↑ DTH	—	↑ IL-1
Vitamin B_6	—	↑ DTH	Increased	↑ IL-2
Folic acid	—	↑ DTH	—	—
Trace Minerals				
Iron	—	↑ DTH ↑ NK cells	Increased	↑ Interferon
Zinc	—	↑ DTH ↑ NK cells	Increased	↑ IL-1
Selenium	—	↑ DTH ↑ NK cells	Increased	—
Copper	—	↑ DTH	Increased	—

* DTH: Delayed-type hypersensitivity response
** NK cells: Natural killer cells
*** IL: Interleukins

The studies have shown that zinc deficiency increases morbidity and mortality after challenge with various pathogenic bacteria in experimental animals. Zinc deficiency in children is associated with increased incidence and severity of acute diarrhoea and lower respiratory tract infection (LRTI). A meta-analysis of clinical trials of zinc supplementation showed that both shorter and longer courses of zinc reduced incidence of pneumonia by 25-40% in various studies[14]. In most studies zinc has been given together with vitamin A, as co-deficiency is common and both nutrients are known to favourably affect immunity. In a recent study from India, zinc supplementation was associated with reduced incidence of severe forms of LRTI in zinc-deficient children aged 6-30 months. Osendarp et al showed that zinc supplementation during first 6 months of life is associated with reduced incidence of acute LRTI especially in those infants who were zinc-deficient[15]. However, administration of zinc to zinc-deficient children with post measles pneumonia did not offer any therapeutic benefit[16]. Excessive intake of zinc supplements should be avoided because it is known to depress immune functions and interfere with copper nutrition. Zinc supplementations have been shown to reduce the mortality of malaria due to *P.falciparum*.

There is evidence to suggest that selenium deficiency may be an important predictor of decreased survival of patients suffering from AIDS[17]. It has been shown that myocarditis due to Coxsackie virus (Keshan disease) is aggravated by dietary deficiency of selenium. However, direct benefits of selenium are difficult to evaluate due to potential interactions between selenium and vitamin E.

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