Review Article:
PROTEIN CALORIE MALNUTRITION AND IMMUNE RESPONSE IN CHILDREN

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ABSTRACT
The fundamental relationship between malnutrition and immunity was initially described as a thymolymphatic deficiency caused by protein calorie malnutrition (PCM). The selective sensitivity of the thymus to nutritional injury is specifically important in the formative phases of the fetal and neonatal immune system. Recent studies suggest that prenatal nutrition and growth during the first of life may predict thymic function in adolescence. Related studies have shown that prenatal zinc deficiency is associated with decreased immune function in later life. The prenatal zinc deficiency is generally accepted that age related in immune response appear to be seen from programmed involution of the thymus. Thymic involution and induction of thymulin secretion from human thymic epithelial cells have obtained with zinc treatment, suggesting that specific nutrients may act as regulatory elements by modulating cellular programs. The potential significance of early nutrition for adaptive immune response in general is also indicated by studies of mucosal immune response to antigens, which have shown that experimental priming at birth ensured both a stronger and a more lasting immune response toward potential pathogens. Malnutrition has an adverse impact on immunological functions and can serve to suppress cell-mediated, humoral, and secretory immune competence. Nutritional immunodeficiencies in human beings appear to respond well to dietary therapy. Micronutrients, trace elements, and vitamins have important regulatory effects on adaptive immune cell function.

Keywords: malnutrition, immune response

INTRODUCTION
PCM (protein calorie malnutrition) is defined as marasmus, characterized by a chronic wasting condition, or kwashiorkor or combined as marasmic kwashiorkor. PCM may involve energy deficiency, protein deficiency, vitamin and mineral deprivation. If prolonged, PCM produces wasting and stunting (Beisel 2007). Malnutrition has an adverse impact on immunological functions and can serve to suppress cell-mediated, humoral, and secretory immune competence. Nutritional immunodeiciencies in human beings appear to respond well to dietary therapy, with improvement in some functions becoming evident within a few days of initiating a refeeding program (Cunningham et al. 1996). Host defense requires energy expenditure, and this rapidly becomes compromised in the malnourished or chronically infected host (Schmidt 1997). Current investigations also describe the thymus as the barometer of malnutrition, are identifying how specific nutrient deficiencies such as zinc correlate with clinical malnutrition and impaired thymic function, and furthermore seek to know how critical molecular processes may be affected (Fraker et al. 2000).

Prenatal undernutrition reflected in intrauterine growth retardation leads to reduced thymopoietin production. The study reported that adolescents who were small for gestational age (SGA) at birth had lower thymopoietin levels when compared with control adolescents who were appropriate for gestational age (AGA) at birth. In both groups, thymopoietin level during adolescence correlated with growth in length during the first year of life (McDade et al. 2001).

MALNUTRITION ON IMMUNE RESPONSE AND INFECTION
The importance of host genetic polymorphism has already been reported for infections such as tuberculosis, which is malnutrition an important risk factor. Host defense requires energy expenditure, and
this rapidly becomes compromised in the malnourished or chronically infected host. Pathogens such as parasitic infections or viruses may easily compromise these resources, and if malnutrition is present, the overall development and expression of immune response are significantly impaired. A critical hypothesis is that conditionally essential nutrient requirements may be associated with key stages of development (Beisel 2000).

Current thinking about the fundamental nature of immune response places major emphasis on the microenvironment. Innate immune cells such as natural killer (NK) cells and NK T cells, monocytes, and dendritic cells influence the pattern of cytokine produced by the adaptive immune system, in part by directly secreting their cytokine products into the microenvironment. Infections trigger initiation of the acute-phase response, affecting nutrient metabolism and modulating cytokine pathways (Gallagher & Daly 2006).

The mechanisms through which nutrients affect immune functions frequently include modulation of the cytokine response and are reflected in changes in the overall cytokine pattern. Cytokines are produced in response to triggering events such as infection and cancer but are also induced in response a wide range of stress signals, including nutrient deprivation. Cytokine response is essential for host defense. If uncontrolled, it can also lead to the extreme state of septic shock, causing loss of lean tissue and body fat. To a lesser degree, some of the observed effects of malnutrition may also involve concurrent subclinical and generalized infectious processes, particularly from opportunistic pathogens acting through mediators common to the acute-phase response, as illustrated in Figure 1. Examples include the effects of nutrient alteration on host immune response associated with human immunodeficiency virus (HIV) infection or parasitic infections (Beisel 2000). Although malnutrition is often considered as mainly in issue for underdeveloped countries, suboptimal nutrition is relatively common in children throughout the world and is a significant cause of susceptibility to infection pathways (Ozkan et al. 1998).

**HOST DEFENSE IN PROTEIN CALORIE MALNUTRITION (PCM)**

PCM distinguished by edema and anemia. A mixture of features of both conditions and gradations of expression are frequently observed among malnourished children (Cunningham et al. 1996). PCM may involve energy deficiency, protein deficiency, vitamin and mineral deprivation. If prolonged, PCM produces wasting and stunting. PCM encompasses a range of protein energy deficiency states, from marasmus to marasmic kwashiorkor. Protein insufficiency alone, with or without infection, causes edema associated with hepatomegaly from fatty infiltration of the liver. The manifestation of clinical malnutrition are related to type, severity, and duration of nutritional impairment and may be subclinical, reversible, or irreversible depending on the availability treatment, presence of other diseases or complicating disorders, and the degree of damage. A wide range of effects is observed that affect many organ systems and specific tissues, requiring integrated clinical management according to the severity and features at presentation (Cunningham et al. 2002).

![Figure 1. Illustration of some of the key interactions that lead to altered immune response in the malnourished host during infectious exposure. IL = interleukin. TSF = tumor necrosis factor.](image)

The effect of nutrient deficiency on immune response and host defense has been primarily studied in PCM and in micronutrient deficiencies. Undernutrition, especially PCM, is clearly associated with increased susceptibility to infections and with greater morbidity from infections. However, the proximate cause of reduced host defense and increased mortality from acute respiratory infections observed in the malnourished child is often related to a combination of factors rather than to a single factor (Lin et al. 1998).

Both marasmus and kwashiorkor are characterized by reduced antioxidant activity, an important component of host defense. Talti and colleagues have described reduced red cell glutathione, and increased lipid
peroxidation in children with marasmus, whereas Reid and colleagues observed decreased erythrocyte glutathione synthesis in kwashiorkor. Although the basis of edema in kwashiorkor is unclear, this is probably linked to increased levels of inflammatory cytokines, specifically IL-6 and C-reactive protein, and to the action of the soluble receptors of tumor necrosis factor (TNF) (Doherty et al. 1999).

Primary malnutrition is associated with atrophy of lymphoid organs and profound immune malfunction leading to susceptibility to pathogens, reactivation of viral infections, and development of opportunistic infections. The effect of malnutrition on T-cell maturation and thymic function is particularly important in children in whom the adaptive immune response is forming. Malnutrition leads directly to thymic involution, revealing the thymus gland as the barometer of malnutrition in children. As suggested by studies comparing AGA and SGA babies, prenatal undernutrition may be generally linked with thymic function in adolescence. Nutritionally caused thymic involution is very similar to congenial thymic aplasia and to the action of the soluble receptors of tumor necrosis factor (TNF) (Doherty et al. 1999).

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Lymphocyte development and differentiation are directly affected by malnutrition as a consequence of thymic deficiency. When T cells from children with severe PCM were compared with those from well-nourished children, immature differentiation was directly associated with thymic involution as measured by echoradiography. Although regrowth of the thymus is longer than restoration of normal body weight when children were fed, this could be significantly hastened by the addition of zinc supplementation. Thymic involution can also occur secondary to infections caused by malnutrition because the thymus is extraordinarily susceptible to stress depletion (Ozkan et al. 1998).

Experimental studies show that the thymus is unusually vulnerable to programmed cell death. Studies in the genetically wasted mouse suggest that the central abnormality may be a high or premature rate of spontaneous apoptosis in the thymocyte population. Possibly related effects have been observed in rats rendered magnesium deficient by diet. In these studies, Malpuech-Brugere and colleagues found acceleration of thymic involution and apoptosis. In these studies, magnesium deficiency caused enhanced inflammation and susceptibility to peroxidation in association with increased apoptosis. Recent studies by Hoffman-Goetz reported that artificial rearing without maternal factors is associated with reduced thymic cell number and weight compared with maternal rearing of rat pups. These studies suggest involvement of the hypothalamic-pituitary-adrenal axis in thymic homeostasis (McDade et al. 2001).

Reported immunologic abnormalities in severely malnourished infants and children have been primarily related to the cellular immune system. Relatively fewer changes in overall immunoglobulin levels have been found, although IgA1 and IgA2 tend to be higher. Rikimaru and colleagues undertook a systematic evaluation of lymphocyte subpopulations and immunoglobulins among normal children and children with kwashiorkor, marasmus, and marasmic kwashiorkor. IgA and C4 were higher, whereas C3 and relative B cell percentage were lower in the severely malnourished groups (McGee & McMurray 2006).

Serum levels of immunoglobulins do not predict specific de novo antibody response, and specific studies suggest that malnutrition affects some immunogens more than others. Stunting appears to be strongly associated with decreased IgG antibody response to measles. Decreased C3, decreased TNF-α, and IL-6 response to lipopolysaccharide stimulation in vitro are also characteristic of malnourished children. Protein deprivation alone may cause reduced phagocytic activity and impaired IL-1 and IL-6 production, while sparing monocyte antigen interaction (Doherty et al. 1998). Experimental studies in the rat have suggested that low dietary protein affects the gut immune system at several levels, including mucosal IgA, secretory component, the number of IgA-containing cells, and the level of IgG. These studies were conducted in the absence of caloric restriction and could be reversed by refeeding. However, the effects of a single grain diet such as maize may also be related to metabolites of dietary constituents rather than to nutrient absence. Current thinking suggests that the high level of linoleic acid in maize in the absence of other polyunsaturated fatty acids in the diet may cause increased production of PGE2, leading to down regulation of Th1 cytokine production (McGee & McMurray 2006).

Some of the effects of PCM might involve endocrine interaction with the immune system. Zamboni and colleagues observed high basal growth hormone (GH) levels but reduced GH receptors in malnourished children. Recent studies have shown that serum leptin levels and insulin-like growth factor I (IGF-I) are reduced in both marasmus and kwashiorkor, suggesting that nutrient deprivation leads to decreased fat mass, insulin, and possibly IGF-1, suppressing leptin, which may in turn stimulate the hypothalamic-
pituitary-adrenal axis to increase cortisol and GH secretion. Related studies have shown that GH could be used therapeutically to restore somatic and muscle growth in an experimental model of PCM. In controls, an enriched diet promoted fat deposition alone. Thymic atrophy in malnutrition leads to loss of cortical CD4+ T cells. Correlation between serum corticosterone level and thymic atrophy has been shown in a murine model of protein malnutrition. Refeeding reversed this effect. These studies suggest that increases in serum corticosterone observed in PCM could also trigger apoptosis, contributing to the loss of differentiated T cells (Gaulsch et al. 1999).

Although the effects of infection and malnutrition on immune response are interactive, the impact of each on immune response is also independent. A recent examination by Mishra and colleagues of graded PCM on immune response is also independent. A recent study in children at risk for *Mycobacterium tuberculosis* infection included study of response to a skin test anergy panel, including PPD. Impaired cellular immunity was found in all grades of malnutrition with the exception of response to PPD in grade 1. Weight loss is a common presenting symptom in children with active *M. tuberculosis* infection. A recent study in adults has shown that before treatment, both leptin and TNF-α levels were elevated and intercorrelated. Although changes in body mass index (BMI) were proportional to change in leptin during treatment and weight gain was achieved early in the course of antibiotic treatment, there was no correlation between BMI and leptin before or after treatment. TNF-α levels did not change. Post-treatment leptin and TNF-α levels did not correlate. Thus, the underlying deregulation of leptin and TNF-α promotes wasting (Beisel 2000).

PCM seriously impairs immune response to some vaccines, such as BCG. Although BCG does not prevent *M. tuberculosis* infection, immunization in endemic environments may inhibit development of invasive disease. However, this protection may be largely ineffective in children with PCM, as shown in a study of immunized malnourished children who did not respond to tuberculin after immunization, became infected, and went on to develop disseminated disease. The control group of well-nourished children was skin test responsive and had a modified disease expression with greater localization and reduced haematogenous spread. In contrast to the impaired reaction of malnourished children to BCG, immune response to other vaccines may be conserved. For example, seroprotection was achieved even in malnourished children with hepatitis B vaccine, although the observed frequency of protective response was reduced compared with that of healthy infants (Schwenk & Macallan 2000).

Response to some pathogens may appear to be improved in some states of malnutrition. Genton and colleagues assessed incidence of malaria in children of Papua New Guinea, and found that increased height for weight at baseline predicted incidence of malaria during the year of study, whereas lymphocyte response to malarial antigens was lower among these wasted children. However, malarial incidence was not different among wellnourished compared with malnourished children, when at stunted children were included in the analysis. Further cytokine production toward malarial antigens was actually greater among the malnourished but not among wasted children, suggesting that a favorable cytokine regulatory shift might be the basis of improved response. Although stunting may be considered an adaptive host response to prolong nutrient deprivation, the stress response is negatively affected, and this would likely have a detrimental effect on immune response in acute infection (Beisel 2000).

Increased incidence of infections is common in PCM. A large longitudinal study, carried out over 1 year among undernourished rural Bangladeshi children, has shown that wasting and skin test anergy indicating immune deficiency were linked to acute upper respiratory infections. Some infections may also be pivotal in enhancing the risk of malnutrition in children. Dale and colleagues have shown that *Helicobacter pylori* infection, common among Gambian children, is strongly associated with other enteric infectious and chronic malnutrition in the postweaning period (Beisel 2000).

**NUTRIENT AND IMMUNE RESPONSE**

Settings in which conditional nutrient requirements have already been identified include surgical stress in which glutamine and arginine are required for immune recovery and conditions of rapid growth in which the impact of dietary nucleotides can be observed. Fundamental questions for the future are likely to focus on the role of host genes as well, for example, those regulating iron uptake and cytokine receptor gene polymorphism (Cunningham & Rundles 2002).

In this discussion, effort will be made to distinguish indirect nutrient effects, which are general and applicable to all tissues, from direct actions in which lymphoid tissues and immune response are affected either disproportionately or specifically. Similarly, the mechanism of nutrient action may differ according to setting and concentration. Pharmacologic use of
micronutrients, trace elements, and vitamins present in a vector have important regulatory effects on adaptive immune cell function. Specific nutrients such as zinc support a Th1 cytokine response in which interleukin (IL-2) and interferon (IFN)-γ are produced, whereas other nutrients, such as vitamin A, typically support secretion of Th2 cytokines, including IL-4, IL-5, and IL-10. Therefore, the overall effect of the microenvironment is to drive immune response toward either a Th1 or a Th2 response (Beisel 2007).

Many nutrients interact with other immune regulatory molecules to influence immune response. Examples include the reported counterregulatory effect of vitamin E on prostaglandin E2 (PGE2) suppression of a cyclic adenosine monophosphate (AMP) response element binding (CREB) protein. Mechanisms of nutrient action often involve several pathways and produce a range of phenotypic effects. In the mouse, vitamin B12 (cobalamin) deficiency reduces levels of C3, immunoglobulin (Ig)M, and IgG and increases production of IgE through causing a shift from Th1 to Th2 response. Increased CD8+ T cell number and NK cell levels of IgE through causing a shift from Th1 to Th2 cytokine response is crucial for the differentiation of adaptive immunity in this period. Low birth weight AGA infants respond well to some immunogens such as Bacille Calmette-Guerin (BCG) with respect to proliferative response to antigen, 1L-2 production in vitro, and skin test response to purified protein derivative (PPD) in vitro. Low birth weight infants also tolerate and respond to immunization with diphtheria-tetanus-pertussis (DTP) but do not respond effectively to Haemophilus influenzae type B. Further maternally acquired passive immunity, assessed as geometric mean antibody to viruses and to bacteria, is reduced. The low birth weight infant is hypogammaglobulinemic and susceptible to nosocomial infections, but intravenous immune gammaglobulin is largely ineffective in reducing these infections. Importantly, studies have also shown that the immune response of the premature infant is also affected by routine blood transfusion to replace blood drawn for clinical monitoring (Carlson & Ziegler 1998).

The effect of nutrients in immune response can
depend on the site of action. For example, the gut associated lymphoid tissue (GALT), thymus, spleen, regional lymph nodes, or immune cells of the circulating blood. The same nutrient may have a different mechanism of action in various sites. For example, zinc may potentiate to Th1 response systemically and to Th2 responses at the level of GALT. Responses are also affected by other host factors, including the presence of infection or other illness, stage of life, age, and antigenic history. With the principal exception of thymulin, the zinc dependent hormone, hormonal changes have been taken into account in studies of immune development. However, current evidence suggests that endocrine factors affect both innate and adaptive immune response (Bengmark 1999).

The immune system has been thought of two essentially separate, innate and adaptive systems responding to the evolving needs of the organism in defense against pathogens. The innate system that mediates in immediate immune reaction that is independent of specific antigens has developed to recognize microbial through identification of conserved microbial products, pathogen-associated molecular patterns, and to know by means of specific gene products. Thus, in addition to unique microbial motifs, infected or pathologically altered self can be identified as missing or altered self. Adaptive immunity has been divided conceptually according to cell type and origin as the response of bone narrow derived B cells belonging to the humoral immune system and thymus derived T cells of the cellular immune system. Through antigen encounter, polyclonal T cell responses become refined to a more restricted T cell to a process that resembles the affinity maturation of B cells. Differentiation of cell function and cell interactions are significantly determined by the local microenvironment. For example, in the liver, immune cells such as natural T cells, which have distinct cytokine secretion patterns affecting host response to antigen. Thymus independent T-cell differentiation is also dominant in the gastrointestinal tract, as mediated by such cells as the intraepithelial lymphocyte (Ozkan et al.1998).

A growing general concern is that nutrient intake may be suboptimal because the diseases of prematurity impose an additional metabolic burden. Assessment of selenium and zinc has shown that levels are low, even when intake follows current guidelines (Fraker et al. 2000). Protein and lipid intake may need to be increased, because the development of the gut and the immune system occurs interactively, it is likely that nutrients may foster normal tolerant immune response toward food antigens. Supplementation with dietary nucleotides has been suggested as a means of beneficially affecting the growth of the gut in the premature infant through influencing intestinal permeability and absorption of macromolecules, affecting antibody response toward β-lactoglobulin and α-casein. Martinez-Augustin and colleagues have found that IgG antibodies against the main antigenic proteins in cows milk were generally higher when nucleotide supplementation was provided. This difference reached significance for antibody to β-lactoglobulin at 30 days of life when gut closure had occurred. Studies by this group also suggest that IgA and IgM humoral immune response are enhanced by nucleotide supplementation (Lin et al.1998).

The neonate requires micronutrients such as iron, zinc and selenium as well as an energy diet. Vitamin A is crucial for development of normal immune response and for development of epithelialization in the lung. Shenai and colleagues have shown that airway infection in the mechanically ventilated very low birth weight infant was associated with reduced plasma vitamin A. Human milk normally provides bioavailable micronutrients such as zinc, as well as secretory immunoglobulin and growth factors. Some maternal milk may be lacking in zinc despite normal levels in serum, and in such cases, babies may develop a condition that is phenotypically identical to acrodermatitis enteropathica. Low levels of fatty acids, such as docosahexaenoic acid (DHA), in mothers have been found to correlate directly with low levels in malnourished children. DHA is critical for visual acuity affect postnatal brain growth, and also
influences immune response through inhibitory effects on the IL-2 pathway. The significance of this for host defense maturation of the immune system requires further study (Kelly & Coutts 2000).

Secretory IgA antibodies in milk reactive against antigens in the maternal gut can be protective against gastrointestinal disease. Recent studies show that live immune mediators in milk such as transfer growth factor (TGF)-ß and soluble CD14, the ban pattern recognition receptor, are likely to be key elements in tempering neonatal immune response. Maternal malnutrition is associated with a decline total milk IgA, C3 and C4 and may affect pass transferred antimicrobial defense. Studies suggest milk antibody levels are to some degree conserved, when maternal nutrition is inadequate. Maternal may also be important in influencing the gradual shift in immune polarity in the neonate from Th2-type systemically and Th1-type response in the GALT toward the adult pattern in which inflammatory immune response is up-regulated in the periphery and Th2 response predominates in the gut (Bengmark S 1999).

Changes in mucosal development occur in the net period in the context of major shifts in enteral intake, microbial exposure, and immune cell maturation. Weaning time of enhanced risk of malnutrition and therefore of increased vulnerability to infections. Normal intestinal growth is sharply enhanced at weaning, and this is mediated through T-cell activation by food substances and microbial antigens and involves transient, localized inflammatory response. Recent studies have shown that this is accompanied by increased expression of the IL-2 receptor and expansion of α/ß T-cell receptor-positive (TCR) + cells (Doherty et al. 1999).

MICRONUTRIENTS AND IMMUNE FUNCTION

Current studies suggest that much of the enhanced susceptibility to infections observed in PCM may be directly related to micronutrient insufficiency. Good and colleagues, who proposed that deficiency of certain key trace element, especially zinc, might be the direct cause of immune deficiency in the malnourished host. Iron, copper, and iodine deficiencies are the most common trace element nutrient deficits in North America. Selenium deficiency, like that of iodine, affects parts of the world with low levels in soil. Micronutrients are often deficient in generalized infections such as chronic viral illnesses and my directly cause impaired immune response (Cunningham & Rundles 2002).

Low dietary intake of antioxidant nutrients can also influence response to infections and may lead to an unopposed inflammatory state. For example, H. pylori can lead to chronic gastritis caused by activated phagocytes. Nair and colleagues observed that patients with gastritis and peptic ulcer disease characteristically have a low level of antioxidants in both serum and mucosa whether or not H. pylori infection was detected. Relevant studies in a mouse model have shown that treatment with antioxidants to reduce gastric inflammation and to lower bacterial load. Bennedsen and colleagues observed a shift from a Th1 type immune response to a mixed Th1/Th2 response, which was dominated by IL-4 and IFN-γ production (Schmidt 1997).

Micronutrients have a crucial impact on immune response, both through antioxidant effects and through modulation of cytokine expression. Trace elements and vitamins perform antioxidant functions through participation in enzyme catalyzed reactions. These reactions are essential to offset potential oxidative damage caused by free radical formation. Three antioxidant enzymes, the copper, zinc and manganese superoxide dismutases, require trace metals for biologic activity, micronutrients are pivotal regulators of cytokine production. Parenteral nutrient preparations may not provide adequate levels of micronutrients such as vitamin E and selenium, causing antioxidant deficiency, which may lead to lipid peroxidation, a measure of oxidative stress (Cunningham & Rundles 2002; Schmidt 1997).

CONCLUSION

Nutrient deficiencies may have an indelible effect during critical periods of early development by exerting an imprinting effect on the fundamental program of future development. This concept is supported by the discovery of interactions between neonatal nutritional status and blood pressure or cognitive ability. In the changing social conditions of childhood in general increasingly fragmented family life, knowledge of nutrients that may affect the development of immune response will have greater critical importance for preventive effort support future host defense against new pathogens.

REFERENCES