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Issue 6

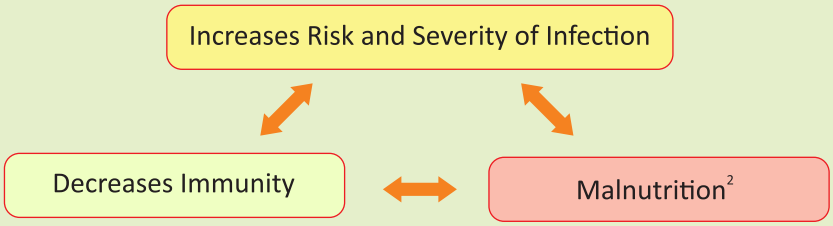
What's **INSIDE**

Role of Proteins in Immune System

Protein Energy Malnutrition and Immune Function

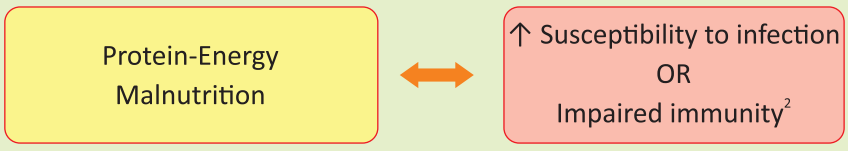
Protein energy malnutrition (PEM) is the most common form of malnutrition.[1] It occurs most frequently in infants and young children, and is commonly associated with infection.[2]

As per World Health Organization, PEM is "an imbalance between the supply of protein and energy and the body's demand for them to ensure optimal growth and function".[3]



- It affects about **800 million people worldwide,** including over 150 million children <5 years of age mostly in developing countries.[1]
- PEM is **a major public health problem in India.**[3]

Worldwide, **PEM** is an important **cause of secondary immune deficiency.**[4]



Immune changes observed in PEM are:

- Innate Immunity: Reduced neutrophil bactericidal activity, low C_3 and CH_{50}, low NK cytotoxicity.
- Adaptive Immunity: Thymic atrophy, peripheral lymphoid atrophy, inverted CD4:CD8 ratio, impaired lymphocyte proliferation to mitogens/antigens, impaired delayed-type hypersensitivity, high IgA, normal IgG.[4]

Depression of cell mediated immunity in PEM occur due to absolute or relative deficiency of amino acids for cell multiplication. Even deficiency of single amino acids have marked defect on antibody production and little defect on T-lymphocyte function.[2]

This immunological impairment can be improved with supplementation of several amino acids, including arginine and glutamine. **Immune system can use these amino acids as a fuel either directly, or by their conversion to other amino acids** (e.g., glutamine) or to glucose.[6]

Role of Proteins and Amino acids in immunity

Amino acids

Amino acids are fundamental building blocks of proteins. Apart from its role in protein synthesis, amino acids also supports various immune cell functions and helps preserves immune responses.[6] They are a key nutrient for immune cells, and their supply instructs immune cell function.[7]

"Amino acids have various immunoregulatory functions."[6]

Amino acids are involved in immune responses such as -[6]

- Synthesis of various proteins, including cytokines and antibodies
- Activation and proliferation of lymphocytes
- Activation of NK cells, and macrophages
- Regulation of intracellular redox states
- Regulation of gene expression

Changes in the **concentrations of amino acids** in the plasma and tissues act as a trigger for **abnormal immune responses** which can cause **malnutrition** and certain pathological conditions such as **infections, malignant neoplasm formation, autoimmunity, and inflammation.**[6]

Amino acids affects the host immune responses against pathogen including, function of innate immune cells (e.g., macrophage), activation and differentiation of T cells and antibodies production by B cells. Hence, changes in the metabolism of amino acids at the infection site can affect the infection outcome. Host can also alter amino acid metabolism after an infection by pathogen.[8]

Branched Chain Amino Acids

Branched-chain amino acids (BCAA) consists of 3 essential amino acids leucine, isoleucine, and valine. These amino acids catalyze the primary steps of degradation and also provide α-amino groups for glutamine synthesis, mainly in skeletal muscle.[6]

BCAA was incorporated by human immune cells into proteins. While, incorporation of isoleucine is greatest into lymphocytes, followed by eosinophils, and neutrophils. For the **synthesis of other amino acids, BCAAs also act as donors of nitrogen and of carbon skeleton,** which are important in supporting immune cell function. Immune system depend on protein synthesis, as an immune response need synthesis of new cells and antigen-presenting machinery, immuneglobulins, cytokines, cytokine receptors, acute phase proteins etc.[9]

"BCAA is essential to support efficient immune function".[9]

Glutamine

Glutamine is the most abundant and versatile amino acid.[10]

Role of Glutamine in Immune Functions:	Essential for lymphocyte proliferation and cytokine production, macrophage phagocytic plus secretory activities, and neutrophil bacterial killing.
	Utilized by immune cells, such as lymphocytes, neutrophils, and macrophages at similar or rates higher than glucose under catabolic conditions, like sepsis, recovery from burns or surgery, and malnutrition, high intensity physical exercise.[10]
	Plays different roles in T cells, which can progressively proliferate after activation, and in non-proliferative phagocytic cells such as macrophages.[6]
	Acts as an energy substrate for leukocytes.
	Important in cell proliferation, tissue repair process activity, and intracellular pathways associated with pathogen recognition.
	Prevent the changes in NADPH oxidase activity and superoxide production induced by adrenaline in neutrophils.
	Required for human B lymphocyte differentiation to plasma cell and to lymphoblastic transformation.[10]

Low glutamine concentration affects the whole body as it provides nitrogen atoms for the synthesis of purines, pyrimidines, and amino sugars. Since, immune cells depend on glutamine availability to survive, proliferate, and function, and to defend the body against pathogens. When, there is glutamine deprivation due to increase glutamine demand during catabolic conditions, it can lead to severe impairment of the immune function.

Thus, **low plasma glutamine availability contribute to the impaired immune function** in various conditions. Depletion of glutamine decreases the lymphocyte proliferation, impairs expression of surface activation proteins on and production of cytokines, and induces apoptosis in these cells.

Glutamine supplementation helps the body to **regulate impaired inflammatory responses** and simultaneously **avoid immunosuppression**. It is **beneficial for patients after surgery, radiation treatment, bone marrow transplantation, or injury** if given through the parenteral route. Glutamine administration **before the onset of infection prevents it,** by preventing amino acid deficiency.[10]

Glutamine clinical nutrition supplementation protocols are recommended for-

- Immune suppressed individuals
- Pre-and post-operative patients
- Many elite athletes to restore immune functions[10]

Arginine

Arginine is a basic amino acid naturally ingested in our diets.[11] It plays a key role in the various biological processes including the immune response.[12]

Role of Arginine in immune Functions:	Sole amino acid substrate for nitric oxide (NO) production by all isoforms of NOS.
	Essential for normal T-cell proliferation and function.[11]
	T-cell receptor complex expression, and memory T-cells development.[11]
	Enhances lymphocytic progress and phagocytosis, and speeds up wound healing.[13]
	Enables normalization of T-cell response after serious surgical procedures and traumas.[13]

Arginine deficiency can cause-

- Progressive **reduction** in in the number of **T-cell receptors** on the cell membrane.
- **T-cell dysfunction** after surgery and trauma which increases the susceptibility to infection.

Arginine depletion can occur with the pathologic production of arginase 1 in myeloid suppressor cells (MSC) which results in compromised T-cell function and NO production that increases the susceptibility to infection. Thus, **arginase 1, plays an important role in regulating the immune functions of activated T cells** by depleting arginine.[11] Arginase 1 has been demonstrated to regulate the bioavailability of arginine to control nitric oxide production through nitric oxide synthase (NOS), particularly by inducible NOS, the only substrate for which is arginine, and also modulates T cell functions similarly.[6]

Dietary arginine supplementation are often used to **boost the immune system.**[11] Arginine supplementation can **reverse the impaired T-cell function** suggesting its immunomodulation capacity.[12] It **prevented thymic involution** after surgery, **increases the number of lymphocytes** and are **required for adequate wound healing.**[11]

Proteins

Protein is a macronutrient required for the development, maintenance and repair of the body cells. It is the frame work of cells, body defense systems, enzymes, and hormones.[13,14]

Protein deficiency can **weaken the immune system.**[13] As, most of the immune mechanisms depend on production of active protein compounds.[14] Decrease in humoral and cell-mediated response and increase in oxidative stress was reported in severe protein and protein-energy deficiency.[15] Thus, **adequate protein consumption is important to keep the immune system strong.**[13]

Bioactive proteins and peptides shows **antimicrobial, antioxidant, antithrombotic, antihypertensive, hypocholesterolemic, hypoglycemic, immunomodulatory, opioid, and antiproliferative** activities. Enhancement in the immune cell functions observed with the immunomodulatory peptides.[16]

Protein Hydrolysates

Protein hydrolysates is a **potent source of bioactive peptides**. Various protein hydrolysates have **immunomodulatory capacities**.

"Protein hydrolysates have immunomodulatory effects in humans."[17]

Functions of protein hydrolysates and bioactive peptides-

- Strengthen the epithelial barrier and enhance the production of mucus and so-called anti-microbial proteins that delete pathogens.
- Enhances IgA production
- Can lead to a more matured and developed immune response
- Possess anti-inflammatory properties.
- Also affects systemic immunity.

Casein hydrolysates reported to have immune effects. Different hydrolysates from casein were found to possess either proliferation increasing or inhibiting effects, showing that individual protein hydrolysates from the same protein source also have remarkably different immunomodulating properties.[17]

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Casein

Casein is one of the major proteins of milk and the major source of amino acids. It have been classified as α-, β- and κ-caseins.[18,19] **Casein proteins and its fragments are multifunctional and exert numerous immunomodulatory action.**[20]

Some of the functions of casein are-

- Promotes the **release of cytokines**
- **Regulation of haematopoiesis and immune response**
- Inhibit the proliferation and induce the differentiation of leukaemia cells.[18]
- **Function as antiviral and immune regulatory factors** by both up-regulation to enhance killing of viruses, and down-regulation to reduce detrimental conditions.[21]
- **Chemoattract immune cells** such as monocytes, act as chaperones
- **Stimulate cellular immune functions** such as macrophage phagocytosis.[20]

PEM is an important cause of secondary immune deficiency. Immune system can use amino acids as a fuel either directly, or by their conversion to other amino acids. Amino acids such as arginine and glutamine can improve immunological impairment. BCAA is essential to support efficient immune function. Glutamine supplementation helps the body to regulate impaired inflammatory responses and simultaneously avoid immunosuppression. While, dietary arginine supplementation are often used to boost the immune system. Also, adequate protein consumption is important to keep the immune system strong. Protein hydrolysates and casein have immunomodulatory effects in humans.

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