proteinews

Issue 4

What's
INSIDE

Role of Proteins in Immune System

Malnutrition and Immunity

Nutrition has an important role for the functioning of the immune system. Both macro and micronutrients are used by the immune system for the synthesis of DNA, RNA and protein.[1]

But, in India greater population are at risk of multiple nutrient deficiencies as reported by Indian dietary surveys and protein is one of them.[2]

About 4%-26% of the population, based on age and region, are at risk of quality protein deficiency.[2]

- This nutritional deficiency is related with impaired immune responses mainly cell-mediated immunity, cytokine production, secretory antibody response and affinity. Hence, under-nutrition has a strong impact on the immune system which is a major factor of immunodeficiency and thereby to higher infection rates.[1]

- **Worldwide, malnutrition is considered to be an important cause of immunodeficiency, affecting about 50% of the population.[3]**
- **Worldwide, around 6 million children die each year due to infections caused by malnutrition due to breakdown in the immune system.[4]**

Malnutrition is a serious health problem common in many parts of the world. Protein energy malnutrition (PEM) is the most common form of malnutrition.[5]

Globally, PEM affects some 800 million people, including over 150 million children <5 years of age, most of them in developing countries.[5]

Protein calorie malnutrition impairs the immunity with detrimental effects on the T-cell system which increases infection and further morbidity and mortality in hospitalized patients.[6]

Malnutrition, Immunity and Infection Cycle

Malnutrition can make a person more susceptible to infection, and infection can contributes to malnutrition, which results in a vicious cycle that leads to the two entities benefiting from each other (Figure 1).

- First one: Synergistic effect which happens when an infection worsens the malnutrition or when the malnutrition decreases the immune response to infection.
- Second effect: Antagonist mechanism which occurs less frequently. This occurs when malnutrition decreases the multiplication of the agent.[3]

Worldwide, malnutrition–infection complex is associated with significant morbidity and mortality.[3]

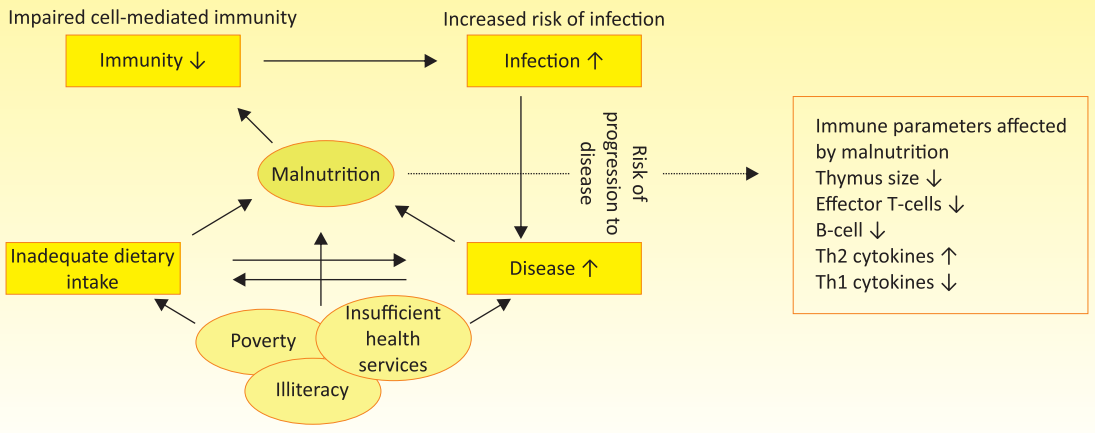
Deficiency of even single nutrient can also alter the immune responses.[8] To reduce the risks of diseases and stay healthy, natural defence system or immunity of the body should be strengthen which can be done by the adequate intake of protein.[4]

Protein

Protein is a macronutrient required for the development, maintenance and repair of the body cells. Insufficient protein can cause various health problems such as kwashiorkor, marasmus, impaired mental health, oedema, organ failure, wasting and shrinkage of muscle tissues, and weakness of immune system.[9]

Most of the immune mechanisms depend on production of active protein compounds or cell replication.[4] Immunoglobulin, or antibodies are formed

Figure 1: Relationship between malnutrition, infection and immunity.[7]



with the help of proteins which helps in fighting against infection.[10] Immune system function decreases in protein deficiency.[4]

Casein and whey protein are the major proteins of milk.

Casein

Casein is the major protein in the milk, constitutes approximately 80% of the proteins.[11] It is the principal source of amino acids.[12] It have been classified as α-, β- and κ-caseins.[13]

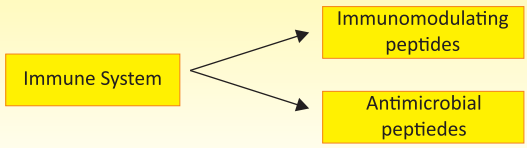
Casein proteins and its fragments regulates the immune response and function as antiviral and immune regulatory factors by both up-regulation to enhance killing of viruses, and down-regulation to reduce detrimental conditions.[14] Some of the functions of casein are-

- Promotes the release of cytokines.
- Regulates haematopoiesis and immune response.
- Inhibit the proliferation and induce the differentiation of leukaemia cells.[15]

Peptides derived from casein possess various physiological roles, such as opioid-like features, immune-stimulation, anti-hypertensive, antibacterial and antiviral effect and also enhances calcium absorption. Its peptides includes -[11]

- Opioid peptides
- Antihypertensive peptides
- Casein phosphopeptides (CPPs)
- Glycomacropeptide (GMP)
- Lactorphins

Figure 2: Bioactive peptides from caseins involved in the immune functions.[16]



β-casomorphin-7 and β-casomorphin-10 derived from bovine-casein stimulate proliferation of human peripheral blood lymphocytes as reported by Kayser and Meisel.[12]

The digestive process of caseins releases its bioactive peptides which are involved in the inhibition or activation of the immune response by acting as agonists or antagonists of opioid receptors.[15]

- Casein phosphopeptides may be of practical use in enteral diets as an immunostimulator to enhance mucosal immunity and host defense.[12]
- Hadden et al. 1991 reported that some peptides from κ-casein and α-lactalbumin are used in immune therapy of human immune deficiency virus infection.[13]

Different casein hydrolysates found to have either proliferation increasing or inhibiting effects, showing remarkably different immunomodulating properties[17] (Table 1).

Table 1: Immune activities of peptides and protein hydrolysates from caseins.[15]

Casein	Derived peptide	Function
αs1-Casein	Trypsin-derived f194-199 C-terminal	Promotes antibody formation and accelerate phagocytosis *in vitro*
κ-Casein	Pepsin/trypsin-derived peptides	Enhances mitogen-induced proliferation of human lymphocytes *in vitro*
β-Casein	FLAb	Immunomodulatory activity that might be related to interactions with monocytes-macrophages and T-helper cells, especially Th-1-like cells *in vitro*
β-Casein	f193-209	Upregulates MHC class II antigen expression on bone marrow-derived macrophages, increasing their phagocytic activity, and induces only a low level of cytokine release
ß-Casein	HLGG	Suppresses the proliferation of lymphocytes

Amino Acids

Proteins are made up of thousands of smaller units called amino acids.[18] For the immune response, muscle protein breakdown to give amino acids for synthesizing new cells, proteins, and peptides. Also, Immune system can use amino acids as a fuel either directly, or by their conversion to other amino acids (e.g., glutamine) or to glucose.

Human immune cells incorporate branched chain amino acids (BCAA) into proteins. For example, isoleucine incorporation is greatest into lymphocytes, followed by eosinophils, and neutrophils. The essentiality of BCAAs for immune cells relates to protein synthesis. Since, the immune system highly depend on protein synthesis for the generation of-

- New cells
- Antigen-presenting machinery
- Immunoglobulin
- Cytokines
- Cytokine receptors
- Acute phase proteins, etc.

These protein synthesis does not occur due to the insufficient BCAAs and so will prevent an optimal immune response from being mounted.[19]

Amino acids has an important role in regulation of the body's immune response. Deficiencies in certain amino acids can result in decreased immune function and a greater chance of developing serious infections. Thus, it is important to maintain sufficient levels of amino acids in the body which can be done either through a balanced diet or with the use of specific supplements depending on the individual.

Currently, amino acids are in use to combat certain diseases which can affect various body systems. It is effective in reducing symptoms without the adverse side effects of addictive drugs and medications. The 3 common amino acids found in the body are glutamine, arginine, and cysteine which have important functions.[18]

Glutamine

Glutamine is the most abundant amino acid in the human body and after glucose it is the most important nutrient for cellular proliferation.[20] Glutamine is utilised at a high rate by cells of the immune system.[18]

The role of glutamine in the immune system are –

- To support optimal lymphocyte proliferation – B-cell differentiation to plasma cells and proliferation of T -cells (Figure 3).[18,20]
- Regulate the rate of IL-2 production and IL-2 receptor expression.[20]
- Production of cytokines by lymphocytes and macrophages.
- Macrophage-mediated phagocytosis is affected its availability.[18]

The lowered plasma glutamine concentrations can contributes to the immunosuppression.[21] Several glutamine-dependent immune responses are disturbed in subjects with low plasma glutamine levels.[18] Supplementation of glutamine after bone marrow transplant, the number of lymphocyte, T-lymphocyte, CD4+ and CD8+ increases.[4]

Thus, a reduced availability of glutamine can increase the susceptibility of humans to infectious diseases by impairing immune function.[22]

Arginine

Arginine is a non-essential amino acid which plays a key role in the various biological processes including the immune response.[20] Dietary arginine supplementation are often used to boost the immune system.[23] The role of arginine in the immune system are-

- Enhances lymphocytic progress and phagocytosis, and speeds up wound healing.[4]
- T-lymphocytes proliferation and z-chain peptide.

- T-cell receptor complex expression, and memory T-cells development.[23]
- Enables normalization of T-cell response after serious surgical procedures and traumas.[4]

It's depletion can suppresses the T-cell proliferation, impaired T-cell functionality and number of T-helper cells decreases[18] (Figure 3).

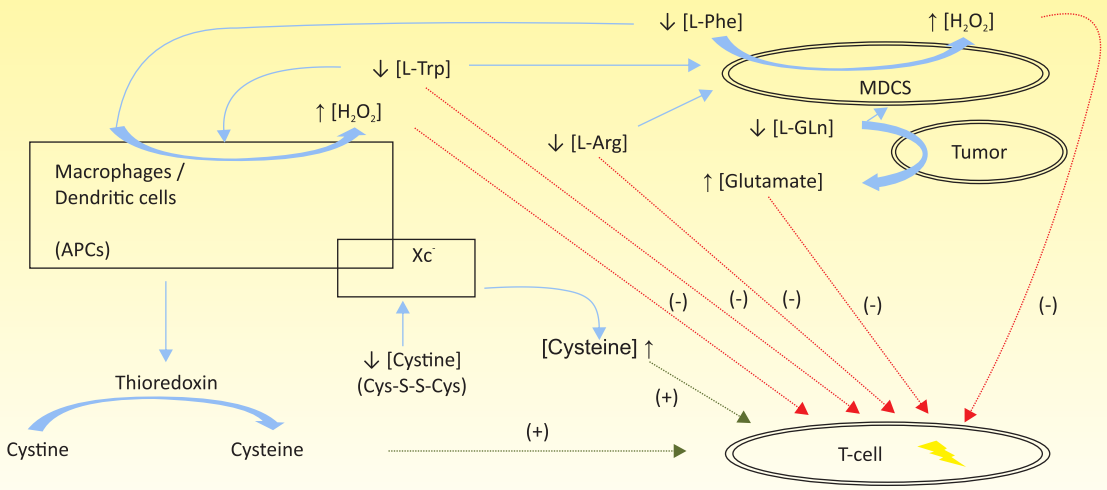
Arginine supplementation can reverse the impaired T-cell function suggesting its immunomodulation capacity.[20]

Cysteine

- Cysteine is another amino acid in chain important for T-cells, as it is a precursor of the tripeptide glutathione.[18] (Figure 3)
- Cysteine is necessary for synthesis of proteins, glutathione and coenzyme A.
- It has been identified as rate limiting for cell growth and proliferation of lymphocytes.
- Number of studies had reported role of cysteine in regulating the proliferation of T-cells.[20]

Insufficient protein in the diet can adversely affect the immune system, particularly on the T-cell system. Supplementation of these amino acids can significantly increase one's capacity to resist infections.[18]

Figure 3: Regulation of T-cell immune responses modulated by amino acid availability.[20]



[Blue plain-arrows signify movement of compounds. Blue block-arrows signify conversion of compounds and transmembrane movement (where applicable). Green dashed arrows signify positive signaling (induction). Red dashed arrows signify negative signaling (inhibition)]

REFERENCES: 1. Kussmann M, Nutrition and Immunity, RSC Food Analysis Monographs. 268-309.; **2.** Minocha S, Thomas T, Kurpad AV, Dietary Protein and the Health-Nutrition-Agriculture Connection in India, J Nutr. 2017;147(7):1243-1250.; **3.** Rodriguez-Morales AJ, Bolívar-Mejía A, Alarcón-Olave C, Calvo-Betancourt LS, Nutrition and Infection, Encyclopedia of Food and Health. 2016; 10.1016/B978-0-12-384947-2.00491-8.; **4.** Karacabey K, Ozdemir N, The Effect of Nutritional Elements on the Immune System, J Obes Wt Loss Ther. 2012; 2: 152.; **5.** Carrillo E, Jimenez MA, Sanchez C, Cunha J, Martins CM, da Paixão Sevá A, et al., Protein malnutrition impairs the immune response and influences the severity of infection in a hamster model of chronic visceral leishmaniasis, PLoS One. 2014 Feb 25;9(2):e89412.; **6.** Daly JM, Reynolds J, Sigal RK, Shou J, Liberman MD, Effect of dietary protein and amino acids on immune function, Crit Care Med. 1990 Feb;18(2 Suppl):S86-93.; **7.** Bapat PR, Satav AR, Husain AA, Shekhawat SD, Kawle AP, Chu JJ, et al. Differential Levels of Alpha-2-Macroglobulin, Haptoglobin and Sero-Transferrin as Adjunct Markers for TB Diagnosis and Disease Progression in the Malnourished Tribal Population of Melghat, India. PLoS One. 2015;10(8):e0133928.; **8.** Ibrahim K.S, El-Sayed, Potential role of nutrients on immunity, International Food Research Journal. 2016; 23(2): 464-474.; **9.** Khan A, Khan S, Jan AA, Khan M, Health complication caused by protein deficiency, J Food Sci Nutr. 2017;1(1):1-2.; **10.** 9 Important Functions of Protein in Your Body, https://www.healthline.com/nutrition/functions-of-protein#section2, last accessed on 31st July 2020.; **11.** Davoodia SH, Shahbazic R, Esmaeilid S, Sohrabvandid S, Mortazaviane AM, Jazayerie S, et al., Health-Related Aspects of Milk Proteins, IJPR. 2016; 15 (3): 573-591.; **12.** Otani H, Kihara Y, Park M, The Immunoenhancing Property of a Dietary Casein Phosphopeptide Preparation in Mice, Food and Agricultural Immunology. 2000; 12:2, 165-173.; **13.** Mohanty DP, Mohapatra S, Misra S, Sahu PS, Milk derived bioactive peptides and their impact on human health - A review, Saudi J Biol Sci. 2016 Sep;23(5):577-83. **14.** Sun H, Jenssen H, Milk Derived Peptides with Immune Stimulating Antiviral Properties, Milk Proteins, InTech, 2012, chp-2; pp.45-82.; **15.** Ledesma-Martínez E, Aguiñiga-Sánchez I, Weiss-Steider B, Rivera-Martínez AR, Santiago-Osorio E, Casein and Peptides Derived from Casein as Antileukaemic Agents, J Oncol. 2019 Sep 8;2019:8150967.; **16.** Petrotos K, Tsakali E, Goulas P, D'Alessandro AG, Casein and Whey Proteins in Human Health, Milk and Dairy Products as Functional Foods, 1st Edition, © 2014 John Wiley & Sons, Ltd, V1, 94-145.; **17.**Kiewiet MBG, Faas MM, de Vos P, Immunomodulatory Protein Hydrolysates and Their Application, Nutrients. 2018;10(7):904.; **18.**How Amino Acids Boost The Immune System, https://aminoacidstudies.org/immune-system/, last accessed on 31st July 2020.; **19.**Calder PC. Branched-chain amino acids and immunity. J Nutr. 2006;136(1 Suppl):288S-93S.; **20.** Sikalidis AK, Amino Acids and Immune Response: A Role for Cysteine, Glutamine, Phenylalanine, Tryptophan and Arginine in T-cell Function and Cancer?, Pathol. Oncol. Res. (2015) 21:9–17.; **21.**Calder PC, Yaqoob P, Glutamine and the immune system, Amino Acids. 1999;17(3):227-241.; **22.** Li P, Yin YL, Li D, Kim SW, Wu G, et al., Amino acids and immune function, Br J Nutr. 2007 Aug;98(2):237-52.; **23.** Popovic PJ, Zeh HJ 3rd, Ochoa JB, Arginine and immunity, J Nutr. 2007;137(6 Suppl 2):1681S-1686S.