**Immunonutrition**

**Background** -

* Systemic inflammatory response, triggered by surgery, trauma, or infection, can impose high metabolic demands on patients, leading to a depletion of essential nutrient stores. 1
* Pro-inflammatory cytokines play a crucial role in enhancing the host's response to injury and infection, which is essential for normal immune functioning.
* Nevertheless, the excessive inflammation caused by pro-inflammatory cytokine production may result in an immunosuppressive effect.
* Furthermore, malnourished patients often experience reduced immune function.

**What is immunonutrition ?**

Immunonutrition can be described as the deliberate adjustment of either the immune system's activity or the outcomes of its activation, achieved through the consumption of nutrients or specific food items in quantities exceeding those typically found in the regular diet.2

**Immunonutrients**

Immunonutrients refer to specific nutrients that have a notable impact on the immune system. Some essential immunonutrients include:

Omega-3 fatty acids

Glutamine

Sulphur-containing amino acids

Antioxidants

Arginine

Nucleotides

These immunonutrients play crucial roles in supporting and enhancing the immune system's functions, contributing to overall health and well-being.

Omega-3 fatty acids exhibit anti-inflammatory properties, effectively countering immunosuppression by down-regulating eicosanoid production.

Sulphur amino acids play a vital role in maintaining antioxidant levels, particularly glutathione, a key antioxidant in the body.

Glutamine is a crucial nutrient for rapidly dividing cells, including those in the immune system, contributing to improved gut barrier function. It also enhances glutathione production, further bolstering antioxidant defenses.3

Arginine stimulates nitric oxide synthesis and growth hormone production, providing an anabolic effect and increasing T helper cell numbers.

Although nucleotides' role is not yet fully defined, they are believed to exert significant effects on T cell function.

**Influence of oxidants on cytokine production-**

In the context of cytokine production, oxidant molecules generated during the inflammatory response play a significant role in up-regulating cytokine production by activating nuclear transcription factors, including nuclear factor kappa B (NFκB), nuclear factor IL-6 (NF-IL-6), and activator protein-1 (AP-1).4

NFκB, a transcription factor, remains in an inactive state in the cell cytoplasm due to its binding with an inhibitory subunit known as IκB. However, when cellular signals are triggered, IκB dissociates, revealing a nuclear recognition site. A series of phosphorylation steps then lead to the movement of the NFκB subunit into the cell nucleus, initiating gene transcription.

Numerous genes are regulated by NFκB, resulting in the production of cytokines, adhesion molecules, enzymes, and other inflammatory mediators. Notably, this dissociation and phosphorylation process includes a redox-sensitive step, wherein oxidant molecules promote NFκB activation, while antioxidants inhibit it.

The up-regulation of NFκB governs many cytokines implicated in inflammatory responses observed during infections and injuries. In fact, several studies have revealed a direct association between increased NFκB activation in sepsis patients and higher mortality rates.

**Antioxidants-**

The body possesses a sophisticated network of interacting antioxidant defenses, safeguarding against oxidant damage. These antioxidants are present in body fluids and various cellular compartments, including cell membranes.

In plasma, several antioxidants derived directly from the diet, such as tocopherols (vitamin E), ascorbic acid (vitamin C), carotenoids like β-carotene and lycopene, and catechins, are found. Additionally, endogenously synthesized proteins and peptides, such as glutathione, ceruloplasmin, albumin, and metallothionein, play crucial roles in antioxidant defense.5

While many of these substances act as antioxidants in the aqueous compartments of cells, vitamin E and carotene predominantly function as antioxidants within cell membranes. The enzymes superoxide dismutase, catalase, and glutathione peroxidase/reductase convert oxidant molecules into harmless by-products.

Nutrients with antioxidant properties, along with those serving as precursors for the mentioned molecules, bolster the body's antioxidant defenses, limiting the direct activation of NFκB by oxidants released during inflammation and protecting host tissue from damage.

Moreover, these nutrients have the potential to mitigate the pathological aspects of cytokine-mediated responses to infection and injury. The complementary action of many antioxidants in oxidation/reduction cycling further enhances their effectiveness.

Micronutrients also play a vital role in influencing antioxidant defenses, as some trace elements are essential components of antioxidant enzymes: copper for ceruloplasmin, copper/zinc/manganese for superoxide dismutases, and selenium for glutathione peroxidase. Together, this comprehensive antioxidant network contributes to the body's ability to counteract oxidative stress effectively.

**Glutathione -**

Glutathione concentrations in various tissues tend to decrease after surgery and during infections, and they have been found to be sub-optimal in several clinical conditions, including human immunodeficiency virus infection, hepatitis C infection, cirrhosis, type II diabetes, ulcerative colitis, and myocardial infarction.

This suggests that the body's antioxidant defenses are depleted as a normal response to trauma and infection. However, there are multiple ways to enhance glutathione synthesis. One straightforward approach involves supplying patients with the three essential amino acids required for glutathione production: glycine, glutamic acid, and cysteine. Glutamine, which can be easily converted to glutamic acid, might contribute to its beneficial effects by supporting glutathione synthesis.

Providing cysteine and methionine to patients is challenging, as these amino acids are not readily taken up by cells. However, cysteine can be administered as n-acetylcysteine (NAC) or pro-cysteine. Several studies have demonstrated the positive effects of glutamine supplementation on patient outcomes, leading to decreased infection rates and reduced hospital stays. This may be attributed to glutamine's ability to maintain glutathione levels while also nourishing the gut and immune system.6

**Fatty acids-**

Fatty acids can significantly impact cell cytokine production and tissue response to cytokines. Dietary fats consist of saturated, monounsaturated, and polyunsaturated fatty acids (PUFA), which can be classified as ω-3 and ω-6 based on their double bond position. Lipids influence the immune system by altering the fatty acid composition of membrane phospholipids in immune and target cells, resulting in the production of prostaglandins and leukotrienes when phospholipases are activated during trauma or infection. Different fatty acids in our diet lead to distinct profiles of released prostaglandins and leukotrienes, influencing the strength of the inflammatory response.

Numerous studies have explored fish oil, rich in ω-3 fatty acids, as an anti-inflammatory agent, focusing mainly on chronic inflammatory diseases like rheumatoid arthritis, psoriasis, asthma, multiple sclerosis, Crohn's disease, and ulcerative colitis. Fish oil has shown to improve inflammatory symptoms and reduce pro-inflammatory cytokine production in both healthy individuals and rheumatoid patients, potentially explaining its anti-inflammatory effects. Moreover, fish oil has demonstrated protective effects against endotoxin, burn injury, and bacterial infection in animal studies. However, it's essential to note that most research has been conducted on chronic inflammatory conditions rather than acute inflammation.

Glutamine is the most abundant free amino acid in the body and plays a vital role in various functions.7 During catabolic stress, muscle stores of glutamine can rapidly deplete. Glutamine is crucial for supporting rapidly dividing immune cells like lymphocytes and neutrophils, aiding in nucleotide synthesis, maintaining gut barrier function by providing fuel for enterocytes, and inducing the production of heat shock proteins. Additionally, it contributes to the synthesis of the endogenous antioxidant glutathione, which may be suboptimal in conditions like HIV, hepatitis C, type 2 diabetes, myocardial infarction, and cirrhosis.

**Glutamine** -

Supplementing with glutamine can protect against oxidative stress effects, especially in intensive care unit (ICU) patients who often exhibit low p-glutathione levels at admission, which correlates with illness severity and mortality rates. Studies have shown promising results of glutamine supplementation in various contexts. For example, in elective surgery patients, it reduced infectious complications and decreased hospital stay length. In critically ill patients, high doses of parenteral glutamine (>0.2g/kg/day) were associated with reduced complications and mortality rates.

To overcome glutamine's low stability in an aqueous environment, it is often combined with another amino acid like glycine or alanine to form a dipeptide. Different dosages of glutamine have been studied, and oral supplementation at 0.3mg/kg/day showed beneficial effects on intestinal integrity. A glutamine-enriched formula (containing 30.5g/100g protein) resulted in decreased infection rates in critically ill patients. However, parenteral administration of 0.4g/kg/day of glutamine decreased leukocyte and natural killer (NK) cell count, potentially suppressing inflammation. Overall, glutamine supplementation has shown promise in enhancing various aspects of health and well-being.8

**Conclusion** -

Nutrient status has the potential to modulate cytokine biology and immune function. Inflammation may inhibit T lymphocyte function.

● Thus any nutrient, which has an anti-inflammatory effect, may enhance T lymphocyte function by removing this inhibitory influence.9

● Nutrients may act at many cellular locations, affecting cytokine production and altering the response of target tissues to cytokines.

● Fatty acids can exert a direct influence by changing membrane phospholipid fatty acid composition.

● Nutrients, which influence antioxidant defences, may alter cytokine production indirectly by modulating the extent of activation of transcription factors by oxidant molecules that are produced during the inflammatory response.10

**References** -

1)Calder PC. Immunonutrition in surgical and critically ill patients. British Journal of Nutrition. 2007 Oct;98(S1):S133-9.

2)Calder PC. Immunonutrition. Bmj. 2003 Jul 17;327(7407):117-8.

3)Bone, RC, Balk, RA, Cerra, FB, Dellinger, RP, Fein, AM, Knaus, WA, Schein, RM & Sibbald, WJ (1997) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 101, 1644–1655.

4)Angus, DC, Linde-Zwirble, WT, Lidicker, J, Clermont, G, Carcillo, J & Pinsky, MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29, 1303–1310.

5)Sadeghi, S, Wallace, FA & Calder, PC (1999) Dietary lipids modify the cytokine response to bacterial lipopolysaccharide in mice. Immunology 96, 404–410.CrossRefGoogle ScholarPubMed

6)Girardin, E, Grau, GE, Dayer, J-M, Roux-Lombard, PJ5 Study Group & Lambert, PH (1998) Tumor necrosis factor and interleukin-1 in the serum of children with severe infectious purpura. N Eng J Med 319, 397–400.

7)Hatherill, M, Tibby, SM, Turner, C, Ratnavel, N & Murdoch, IA (2000) Procalcitonin and cytokine levels: relationship to organ failure and mortality in pediatric septic shock. Crit Care Med 28, 2591–2594.

8)Arnalich, F, Garcia-Palomero, E, Lopez, J, Jimenez, M, Madero, R, Renart, J, Vazquez, JJ & Montiel, C (2000) Predictive value of nuclear factor κB activity and plasma cytokine levels in patients with sepsis. Infect Immun 68, 1942–1945.CrossRefGoogle ScholarPubMed

9)Grbic, JT, Mannick, JA, Gough, DB & Rodrick, ML (1991) The role of prostaglandin E2 in immune suppression following injury. Ann Surg 214, 253–263.

10)Ertel, W, Morrison, MH, Meldrum, DR, Ayala, A & Chaudry, IH (1992) Ibuprofen restores cellular immunity and decreases susceptibility to sepsis following hemorrhage. J Surg Res 53, 55–61.