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Educational Paper

Basics in clinical nutrition: Immunonutrition – Nutrients which influence immunity: Effect and mechanism of action

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1. Learning objectives

- To understand what is meant by the term immunonutrition.
- To be aware of the range of immunonutrients that are available.
- To understand the importance of anti-oxidant defences in immune function.
- To understand how ω-3 fatty acids act.

The systemic inflammatory response, which occurs as a result of surgery, trauma or infection, may exert high metabolic demands upon patients and lead to a depletion of essential nutrient stores. Pro-inflammatory cytokines orchestrate the host response to injury and infection and are crucial for normal immune responses. However, the high levels of inflammation induced by pro-inflammatory cytokine production may exert an immunosuppressive effect. Malnourished patients have reduced immune function. This chapter describes the modulatory role that nutrients exert on immune function, and how immunonutrition may improve immune function.

Immunonutrition can be defined as modulation of either the activity of the immune system, or modulation of the consequences of activation of the immune system, by nutrients or specific food items fed in amounts above those normally encountered in the diet.[5]

2. Immunonutrients

Immunonutrients are nutrients, which have an effect on the immune system. There are many nutrients, which could fall within this definition, but in this manuscript I will confine discussion to ω-3 ($n-3$) fatty acids, glutamine, sulphur containing amino acids, anti-oxidants, arginine and nucleotides. The actions of these substances and their mechanisms of action are summarized in Table 1.

- The ω-3 fatty acids, have anti-inflammatory actions, which will help to reverse immunosuppression by down-regulating eicosanoid production.
- Sulphur amino acids enhance antioxidant status by maintaining concentrations of glutathione, one of the key anti-oxidants in the body.
- Glutamine is an important nutrient for rapidly dividing cells, such as those of the immune system and helps to improve gut carrier function. Glutamine also enhances glutathione production thereby improving anti-oxidant status.
- Arginine stimulates nitric oxide synthesis, and growth hormone production. It therefore has an anabolic effect, and also increases T helper cell numbers.
- Nucleotides currently have a less well defined role, but it is suspected that they have important effects upon T cell function.

There have been a number of key meta-analyses published recently in an attempt to clarify current status as to efficacy of some

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Table 1
Nutrients, which influence immunity and their effects and mechanisms of action

Immunonutrient	Influence on inflammation and immune function	Possible mechanism(s)	Effects
Omega 3 polyunsaturated fatty acids	Inhibits inflammation, enhances T cell functions	Changes in membrane phospholipids	Changes in cytokine and lipid-derived mediator production
Sulphur amino acids and related compounds	Inhibits inflammation enhances T cell function	Suppression of oxidant effects and NFkB activation	Maintenance of glutathione status
Arginine	Enhances T cell function	Stimulation of growth hormone production	Altered nitric oxide production?
Glutamine	Stimulates T cell function, inhibits inflammation?	Stimulation of glutethione synthesis?	Enhances cell proliferation, increases

of these compounds. These studies suggest that immunonutrient mixtures, which contain one or more of the ω-3 fatty acids, glutamine, arginine and nucleotides, are of benefit in specific groups of patients. A reduction in hospital length of stay and infection rates was observed. However, mortality was not reduced. Immunonutrition does not work in all patient groups probably due to the way in which they are fed, the amounts fed, the timing of feeding and individual genetic factors.

3. Influence of oxidants on cytokine production

Oxidant molecules, produced during the inflammatory response, up-regulate cytokine production through the activation of nuclear transcription factors such as nuclear factor kappa B (NFκB), nuclear factor IL-6 (NF-IL-6) and activator protein-1 (AP-1).

The transcription factor NFκB pre-exists within the cell cytoplasm in an inactive form, by virtue of its binding to an inhibitory sub-unit, termed IκB. Cellular signals induce dissociation of the IκB, to reveal a nuclear recognition site, which, after a series of phosphorylation steps causes the NFκB sub-unit to move into the cell nucleus and turns on gene transcription. There are large ranges of genes, which have been shown to be regulated through NFκB. Their products include, cytokines, adhesion molecules, enzymes and other inflammatory mediators. The process of dissociation and phosphorylation has a redox sensitive step, which means that oxidant molecules promote NFκB activation and antioxidants inhibit it.

Up-regulation of NFκB controls many of the cytokines implicated in the inflammatory responses that seen during infection and injury. Indeed, three separate investigators have shown that increased NFκB activation in patients with sepsis is associated with increased mortality rates.

4. Antioxidants

The body has a complex array of interacting antioxidant defences to provide protection from oxidant damage. These antioxidants are present in body fluids and within various compartments of the cell, including cell membranes. Within plasma several antioxidant molecules are derived directly from the diet are found, such as tocopherols (vitamin E), ascorbic acid (vitamin C), carotenoids – β-carotene and lycopene, catechins. In addition, proteins and peptides, that are important in antioxidant defence, such as glutathione, caeruloplasmin, albumin, and metallothionein, are present, which are synthesised endogenously. Many of these substances act as antioxidants within aqueous compartments of the cell, although vitamin E and carotene are the predominant antioxidants within the cell membranes. Superoxide dismutase, catalase, glutathione peroxidase/reductase, convert oxidant molecules to harmless by-products. Nutrients with anti-oxidant properties and those which are precursors for the molecules described above contribute to the body's antioxidant defences and thereby limit the ability of oxidants, released during inflammation, to activate NFκB directly or damage host tissue.

These nutrients therefore may be able to limit pathological aspects of the cytokine-mediated responses to infection and injury. Many of the antioxidants act in a complementary fashion in oxidation/reduction cycling. Micronutrients also influence antioxidant defences since some of these trace elements are present in antioxidant enzymes: caeruloplasmin (copper), superoxide dismutases (copper, zinc, manganese), and glutathione peroxidase (selenium).

5. Glutathione

Given the interaction of antioxidant defences and the dependence within the system on oxidant cycling, it is important to consider that what happens if one component of these antioxidant defences decreases in concentration. A study, which investigated this, gave rats diethylmaleate, a drug, which binds onto glutathione and blocks normal function. Both treated and untreated animals then received similar doses of TNF-α. Animals, who did not receive diethylmaleate and hence had adequate antioxidant defences, experienced no mortality, however, the rats which had impaired glutathione function, experienced high mortality rates. Does a similar situation happen in patients? We have already seen that excessive activation of NFκB confers a bad prognosis. Cowley et al.[4] investigated the total antioxidant potential in a group of patients with severe sepsis and secondary organ dysfunction. Total antioxidant potential gives a measure of the ability of blood to quench oxidant reactions by all antioxidant sources. The study showed a large fall in total antioxidant potential with the onset of organ failure. In patients who ultimately survived antioxidant potential returned to within the normal range but in those who died, the increase in antioxidant potential was much smaller and did not return to normal. Impairment of antioxidant defences therefore carries with it an increased risk of mortality.

Glutathione concentrations in a wide range of tissues decrease after surgery, during infection and have been shown to be suboptimal in a wide range of clinical conditions including human immunodeficiency virus infection, hepatitis C infection, cirrhosis, type II diabetes, ulcerative colitis and myocardial infarction. It therefore seems that the normal response to trauma of any sort, and infection results in depletion of antioxidant defences.

There are many ways of boosting glutathione synthesis. It can be achieved simply by supplying patients with the three amino acids need to make glutathione, i.e. glycine, glutamic acid and cysteine. Glutamine is easily converted to glutamic acid. This may be one of the ways in which glutamine produces its beneficial effect by providing glutamic acid for glutathione synthesis. It is very difficult to give cysteine and methionine to patients since these amino acids are not easily taken up by cells. However, cysteine can be supplied as *n*-acetylcysteine (NAC) or pro-cysteine.

There have been a few studies in which NAC has been used to boost intracellular cysteine concentration. The effect of NAC on the early response and outcome from septic shock was reported by Rank et al.[14]; Spapen et al.[17]; and Paterson et al.[13] These studies

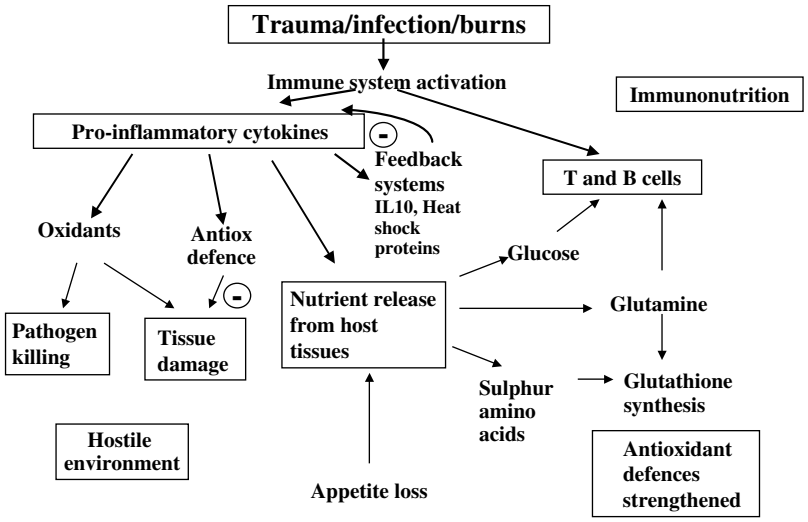

Fig. 1. The influence of metabolic changes during the inflammatory response on anti-oxidant status and immune function.

were not powered to show any effect on mortality, however, the number of days patients were in the intensive care unit decreased, and ventilator requirements were reduced. In another study IL-8 concentrations were reduced substantially in patients who received NAC suggesting that an effect on the activation of NFκB is probably the underlying mechanism. Larger studies are clearly required to assess the effect of glutathione repletion on the high degree of mortality in patients with severe sepsis.

A number of studies have shown beneficial effects of glutamine supplementation on patient outcome with decreased infection rates and reduced hospital length of stay observed. It may be that glutamine is exerting its effects by helping to maintain glutathione status as well as nourishing the gut and immune system.

6. Fatty acids

Fatty acids may influence the ability of cells to produce cytokines and the ability of target tissues to respond to cytokines. The fatty acids in dietary fat consist of three main types according to chemical composition, namely saturated, monounsaturated and polyunsaturated fatty acids (PUFA). PUFA can be sub-divided into two types according to the position of the double bonds in the molecule. The classification of ω-3 and ω-6 (or $n-3$ and $n-6$, respectively) results.

There have been many studies, mostly in animal models, using several of fats. The studies have examined the effects of dietary fat on burn injury, cytokine-, and endotoxin-induced anorexia and fever, cytokine- and endotoxin-induced changes in visceral protein metabolism, and cytokine production from macrophages. In summary, fats rich in ω-3 fatty acids, or monounsaturated fatty acids, or poor in ω-6 fatty acids reduce responsiveness to cytokines and inflammation. Fats rich in ω-6-fatty acids exert the opposite effect. The exception to this rule is evening primrose oil, which, although rich in the ω-6-fatty acid linolenic acid, has an anti-inflammatory effect. The impact of these fatty acids on immune function has been comprehensively reviewed by Miles and Calder[10] (see Fig. 1).

The mechanism of action whereby lipids modulate the immune system is fairly straightforward. Our dietary intake of monounsaturated fatty acids or different types of polyunsaturated fatty acids dictates the fatty acid composition of membrane phospholipids in the immune cells and target tissue cells upon which cytokines act. Under the action of phospholipases, which are activated as a part of the response to trauma or infection, prostaglandins and leukotrienes are produced. Wide ranges of physiological and metabolic changes ensue. Feeding different fatty acids will result in different profiles of released prostaglandin and leukotriene, which will have some impact on the strength of the inflammatory response. A number of studies in particular have looked at fish oil (rich in ω-3 fatty acids) as an anti-inflammatory agent. All of these studies were performed in patients with chronic inflammatory disease rather than the acute inflammation. Inflammatory symptoms were improved by fish oil in diseases such as rheumatoid arthritis, psoriasis, asthma, multiple sclerosis, Crohn's disease, and ulcerative colitis. Fish oil reduces the ability of leucocytes from healthy subjects and rheumatoid patients to produce several pro-inflammatory cytokines and may partly explain the anti-inflammatory effects of fish oil. Fish oil also confers a degree protection in animals against the lethal effects of endotoxin, burn injury, and bacterial infection.

Mixtures of fatty acids have also been administered – in particular 'SMOF' which is a mixture of soya bean oil, olive oil, fish oil and medium chain triglyceride oil. Schulzki et al.[16] fed a group of surgical patient's isonitrogenously and isocalorically with SMOF in a double blind randomised study. Feeding SMOF reduced the ratio of leukotrienes B4 to leukotrienes B5 produced by peripheral blood mononuclear cells in the patients. Leukotriene B5 is a much less potent form of leukotrienes, than LTB4. Hospital length of stay was reduced by 2 days in patients treated with SMOF.

7. Summary

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. 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.

Conflict of interest

There is no conflict of interest.

Further reading

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