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THE IMMUNE SYSTEM AND NUTRITION

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This article will summarise the salient points in relation to antiviral immune function and nutrition, within a backdrop of COVID-19.

Nutrition and immunity together have become a seminal topic, particularly at the current time with the coronavirus pandemic continuing to affect everyone worldwide. The year 2020 was difficult for misinformation in science and epidemiology, but especially for nutrition. How many times did you read that specific nutrients could help to "boost your immune system"?

First off, here's a whistle-stop refresher tour of the immune system and its function and how nutrition fits into it all. The points and information summarised here were taken from the British Nutrition Foundation's annual seminar in November 2020, entitled 'Nutrition and COVID-19'. Dr Philip Calder presented on this and has published an excellent piece in the *BMJ* entitled 'Nutrition, immunity and COVID-19'.[1]

HOW THE IMMUNE SYSTEM FUNCTIONS

There are four lines of defence that the body has in reducing infection/pathogen invasion:

1 Barrier function

This prevents pathogens from entering the body.

- Physical barriers include skin, GI tract, respiratory tract and genitourinary tract.
- Chemical barriers include the acid pH of the stomach.
- Biological barriers include:
  - beneficial bacteria in GI tract or on skin;
  - secretions like secretory IgA in the GI tract, antimicrobial proteins in saliva and tears;
  - complement system.

2 Identifying pathogens if they breech a barrier

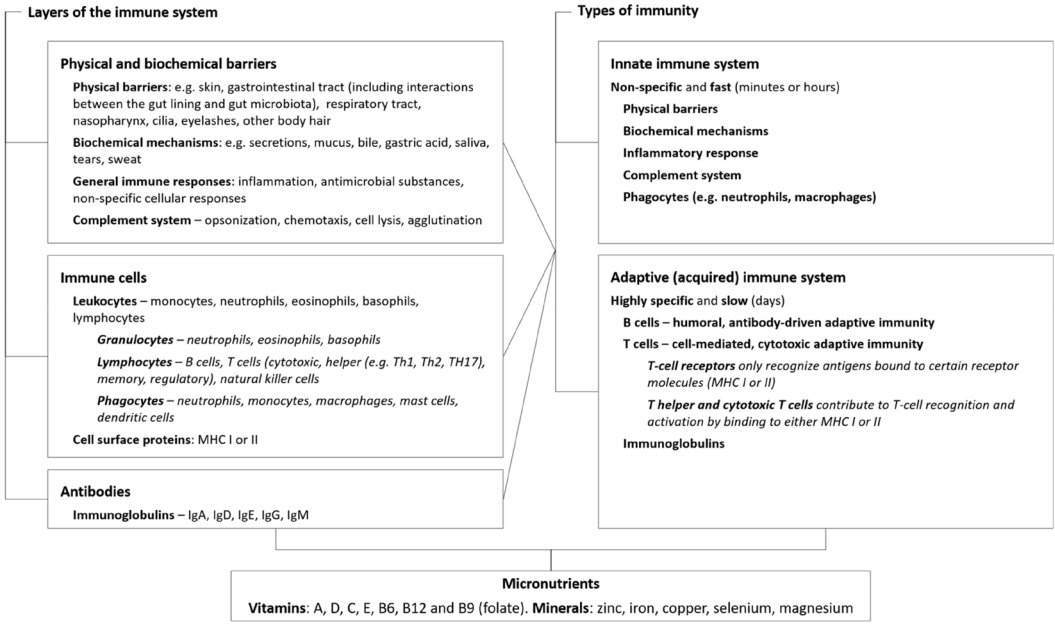
Pathogens are recognised by the innate immune system and possibly by memory cells of the adaptive immune system if there has been an infection before or vaccination.

3 Eliminating pathogens

The immune system uses different approaches to different pathogens in the body. For example, bacteria (which don't typically invade host cells) will be engulfed and killed by phagocytic cells from the innate immune system, digesting the bacteria and displaying their remnants, known as antigens, on their surface. These antigens are recognised by the adaptive immune system, which is triggered by CD4+ T helper lymphocytes to coordinate the response. The response involves both T and B lymphocytes, which are involved in producing antigen-specific antibodies, and the further communication with and activation of the innate immune system.

Viral infection response (for example as in coronavirus which is a single-strand RNA virus) is slightly different in that the

Figure 1: Four lines of defence and the immune system[2]



adaptive immune system is more involved, with CD8+ T lymphocytes and Natural Killer Cells recognising the virus and killing the infected host cells. The virus escapes once the host cell is killed and continues to infect other host cells – the battle continues until the virus is destroyed. This can take days to weeks.

Both types of infection need to have a coordinated response and there is much cell communication, cell proliferation and hormonal/cytokine response impacted by nutrition.

4 Generating an immunological memory

Antibodies can remain in circulation for many months to years, protecting against reinfection. After an active immune response to viral/bacterial infection, a small number of memory T and B lymphocytes remain in a resting state until the same pathogen is identified. They can then rapidly kill the pathogen. Memory cells have a long life – this is the basis of vaccination.

NUTRITION IS INTEGRAL TO THE IMMUNE SYSTEM

Once the immune system is activated, a vast amount of energy and nutrients are needed to support the immune response adequately.[3]

- Fuel is needed for energy, which comes from our diet.
- Biosynthesis – building blocks are needed for cell proliferation and cytokine and protein production, eg, amino acids for immunoglobulins and nucleic acids, cytokines, receptors and acute phase proteins.
- Regulators of molecular and cellular components of immune responses, eg, zinc and vitamin A.
- Substrates for the synthesis of metabolites involved in the immune response, eg, arginine and nitric oxide which is toxic to bacteria.
- Specific anti-infection roles such as zinc.
- Protection of the host tissues against oxidative stress, eg, vitamins C, E, cysteine, zinc, copper, selenium and phytochemicals are involved in this protection.
- Regulation of the immune response via the gut microbiota.

IMPORTANT NUTRIENTS IN THE CONTEXT OF VIRAL INFECTIONS

The nutrients vitamin D, selenium and zinc, are well studied and thought to be most important in terms of their roles in antiviral protection.[3]

Table 1: Important dietary sources of nutrients supporting the immune system[1]

Nutrient	Good dietary sources
Vitamin A (or equivalents)	Milk and cheese, eggs, liver, oily fish, fortified cereals, dark orange or green vegetables (eg, carrots, sweet potatoes, pumpkin, squash, kale, spinach, broccoli), orange fruits (eg, apricots, peaches, papaya, mango, cantaloupe melon), tomato juice
Vitamin B6	Fish, poultry, meat, eggs, wholegrain cereals, fortified cereals, many vegetables (especially green leafy) and fruits, soya beans, tofu, yeast extract
Vitamin B12	Fish, meat, some shellfish, milk and cheese, eggs, fortified breakfast cereals, yeast extract
Folate	Broccoli, Brussels sprouts, green leafy vegetables (spinach, kale, cabbage), peas, chickpeas, fortified cereals
Vitamin C	Oranges and orange juice, red and green peppers, strawberries, blackcurrants, kiwi, broccoli, Brussels sprouts, potatoes
Vitamin D	Oily fish, liver, eggs, fortified foods (spreads and some breakfast cereals)
Vitamin E	Many vegetable oils, nuts and seeds, wheatgerm (in cereals)
Zinc	Shellfish, meat, cheese, some grains and seeds, cereals, seeded or wholegrain breads
Selenium	Fish, shellfish, meat, eggs, some nuts (especially Brazil nuts)
Iron	Meat, liver, beans, nuts, dried fruit (eg, apricots), wholegrains (eg, brown rice), fortified cereals, most dark green leafy vegetables (spinach, kale)
Copper	Shellfish, nuts, liver, some vegetables
Essential amino acids	Meat, poultry, fish, eggs, milk and cheese, soya, nuts and seeds, pulses
Essential fatty acids	Many seeds, nuts and vegetable oils
Long-chain omega-3 fatty acids (EPA and DHA*)	Oily fish

*EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid

Vitamin D

Vitamin D receptors have been identified in most immune cells, and some cells of the immune system (such as dendritic cells) can activate 25-OH vitamin D. It has been shown to impact widely on both the adaptive and innate immune system. There is a great deal of complexity in the way it works in the immune system, both 'boosting' responses from the innate immune system and inhibiting those from the adaptive immune system's T and B lymphocytes.[4] This is but one example of why the message about boosting the immune system is incorrect, and why the immune system needs to be in balance.

An interesting example of the importance of vitamin D, particularly in relation to viruses, is its production of an antimicrobial peptide LL-37, cathelicidin, which is important in antiviral defences.[5]

A study on vitamin D status and lung infection across the seasons in British adults showed an inverse dose response association between vitamin D status and respiratory infection, with the highest infection risk seen in those with serum levels of 25-OH vitamin D at <25nmol/l.[6]

Martineau et al demonstrated the likely effect of vitamin D on respiratory tract infections with a well-considered meta-analysis from 2017.[7] This looked at 25 placebo RCT trials, n=11,321, with both adults and children included in the analysis. There were different doses used over different time periods (weeks to months). Studies with daily dosing used 7.5 to 100mcg. The results clearly showed a significant effect of vitamin D supplementation on reducing respiratory tract infection over placebo. Effects were greatest in those who were vitamin D deficient.

Research published earlier this year by Merzon et al[8] has pointed towards vitamin D status as being likely to affect risk of COVID-19 infection. Suboptimal vitamin D levels were identified as one of four independent risk factors for contracting the virus, and possibly independent risk factors for hospitalisation with COVID-19 (thus increased severity). However, with adjustment to this regression data, vitamin D was no longer significant; nevertheless, the trend remained important.

Vitamin D is highly likely to be an important nutrient in the antiviral immune response, but is usually at suboptimal levels over the winter months in most UK residents, particularly in those who are housebound or who are from ethnic minorities. Therefore, the announcement that care home residents and clinically vulnerable patients will receive free prescriptions of vitamin D in the UK has been a welcome addition to the UK Government's pandemic response.

A healthy balanced diet with a plentiful supply of a variety of fruit and vegetables, is likely to be best to support the immune system, much like the current dietary guidelines.

Zinc

Zinc has a myriad of important integral roles in the immune system and has been well studied.[9] It is integral to metalloenzymes and proteases making it essential to their function. Zinc deficiency has a marked impact on bone marrow, decreasing the number of immune precursor cells, and causes thymic atrophy.[1-4] Zinc is important in maintaining T and B lymphocyte numbers.[4]

In research trials, markers of immune response can be increased with zinc supplementation, particularly in older people and those with low zinc status.[4] It is important to note, however, that high doses of zinc have been shown to impair lymphocyte proliferation and response; therefore, the therapeutic window is yet to be established.[4]

Zinc's therapeutic effects in severe infection have been demonstrated. In a study of patients with severe pneumonia, for example, zinc was shown to reduce risk of mortality.[10]

In terms of COVID-19 infection, as coronavirus is a single-strand RNA virus, zinc is likely to be directly involved in inhibiting the replication process of its genome, as zinc acts to inhibit RNA-dependent RNA polymerase.[11]

Selenium

Selenium supports antigen presenting cells, T cells and B cells, to function. Deficiency has been shown extensively in mice studies to increase susceptibility to viral infections, permitting viruses to mutate, or allowing viruses to become more virulent.[3]

In a trial conducted in Liverpool in 2004, adults with low selenium status were randomised to receive selenium of 50mcg/d, 100mcg/d, or placebo for three weeks, after they received live poliovirus vaccination. Results showed that the ability of the immune system to produce interferon-gamma (an important cytokine in antiviral protection) improved seven days after vaccination, increasing in a dose-response manner after polio vaccination.[12] Researchers also showed supplementation may have resulted in better clearance of the virus and prevention of viral mutations, as these occurred in the control group, but not in the group that received the higher doses of selenium.[12]

An interesting association was also shown between selenium status and COVID-19 cure rate in China.[13] In a population with the highest selenium status, the cure rate of COVID-19 was highest.[13]

Recently, German researchers showed deficiency of selenium may have an impact on COVID-19 mortality. The selenium status was significantly higher in samples from surviving COVID patients as compared with non-survivors, recovering with time in survivors while remaining low, or even declining in non-survivors.[14]

PROBIOTICS AND THE GUT MICROBIOME

The gut microbiota are understood to play a role in host immune defence by creating a barrier against colonisation by pathogens. There is now evidence that probiotics, in particular some lactobacilli and bifidobacteria, can contribute to maintenance of the host's gastrointestinal barrier and reduce the incidence and severity of respiratory infections in humans.[15-18]

Dietary fibre and phytochemicals are fuel for beneficial bacteria and help them to grow in number. A recent American Gut study suggests including over 30 different plant-based foods per week, although portion size has not been elucidated.[19] This would also serve to increase vitamin C intake with diet.

OTHER IMPORTANT EFFECTS TO CONSIDER

We have not had space here to discuss the important effects of ageing on the immune system (known as immunosenescence) and obesity. These are vital considerations for nutrition professionals in providing individualised advice to patients.

CONCLUSION

A healthy balanced diet with a plentiful supply of a variety of fruit and vegetables, is likely to be best to support the immune system, much like the current dietary guidelines. There are a number of other lifestyle factors to consider in addition when thinking about optimising immune health, alongside nutrition.

The problem with misinformation online and statements like "immune-boosting" if used by healthcare professionals, is that this legitimises bogus health claims used to advertise supplements, where there is little evidence to support these in reality.[20]

There is evidence to support the additional supplementation of vitamin D over the winter months, and perhaps zinc and selenium during infection. However, the best dose and time of supplementation is not yet known, and high doses are best avoided due to possible negative effects on the immune system.

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NETWORK HEALTH DIGEST

Questions relating to: *The immune system and nutrition* *Type your answers below, download and save or print for your records, or print and complete by hand.*	
Q.1	Explain the biological barrier functions of the immune system.
A	
Q.2	How does the immune system respond to bacteria?
A	
Q.3	Explain the 'battle' that takes place between our immune system and a viral infection like a coronavirus.
A	
Q.4	What is the role of a memory cell?
A	
Q.5	Why is vitamin D important in our body's fight against viral infections?
A	
Q.6	What role does zinc play?
A	
Q.7	Outline the importance of selenium in protecting against viruses.
A	
Q.8	Describe how probiotics can create a barrier function.
Please type additional notes here.	