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Micronutrients & COVID-19

The evidence-base supporting advice for at-risk groups

The COVID-19 pandemic has brought forth multiple voices advising particular dietary strategies to combat the disease. Although many do so with the best of intentions, some may have personal biases or financial conflicts of interest. Here we summarise the evidence surrounding the role of some of the key micronutrients in infectious disease with a focus on respiratory conditions.

Introduction

In higher income countries, when we discuss dietary patterns, improvements and adequacy, we often focus on the macronutrient profile of the diet. In many cases, this is based on an assumption that the majority of the population are not suffering from micronutrient deficiencies. In regular clinical practice, there are a handful of micronutrients that we tend to pay more attention to, such as iron, calcium, vitamin B12 and vitamin D. In the UK, our knowledge of population micronutrient intakes and status is largely informed by the National Diet and Nutrition Survey (NDNS) which highlights the number of people in our society who are not achieving their reference nutrient intakes (RNI – the amount required to meet the needs of 97.5% of the population) of specified micronutrients. It is widely accepted that malnutrition plays a significant role the body's immune response to disease,[1] but not always clear how important micronutrients are in achieving good clinical outcomes. It is worth noting, the bidirectional relationship existing between nutrition and infection, whereby poor nutritional status predisposes to infection and infection is exacerbated by poor nutritional status.

Vitamin A

Vitamin A plays a role in the regulation of the innate immune response (through natural killer (NK) cells, macrophages and neutrophils), as well as cell-mediated immunity (through the growth and differentiation of B cells).[2] It is also active in humoral antibody immunity and in cytokine signalling, with a role in the inflammatory response as a result.[3] Vitamin A can play a role in the integrity of the mucosal epithelium meaning a deficiency may increase the likelihood of infection via the eyes, respiratory tract or gastrointestinal (GI) tract.[3] Whilst there is some evidence that suggests supplementation may reduce all-cause mortality from infectious disease. However, the majority of these studies were carried out in lesser resourced settings and there may therefore be other confounding factors.

Vitamin C & E

Vitamins C and E are often considered side-by-side due to their combined effects. Like vitamin A, vitamin E plays a role in cell membrane integrity especially in relation to free radical damage.[4] While free radicals are formed in the body through regular metabolism, they may also be formed by processes such as smoking, exposure to chemicals and radiation, and an accumulation can lead to increased oxidative stress.[5] This may cause DNA or cellular damage, either making the host more susceptible to viral infection or adding to oxidative stress in case of a viral infection.[6] Additionally, α-tocopherol (which is the most biologically active form of vitamin E) has been shown to contribute to a healthy immune response in ageing and to reduce upper respiratory tract infections in care home residents.[7]

One of the main roles of vitamin C meanwhile is its ability to regenerate vitamin E.[8] However, it also improves the function of the epithelial barrier.[9] Deficiencies lead to impaired immunity and higher infection susceptibility, increasing the risk of contracting pneumonia.[10] Vitamin C supplementation may contribute towards the prevention and treatment of respiratory tract infections,[11] (RTIs) as well as symptoms of common cold.[12]

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Vitamin D

Observational data has long suggested a link between vitamin D status and the incidence of airway infection. This may be especially true for low status and the susceptibility to RTIs. It is involved in the innate immune response in its role of producing cathelicidin, an antimicrobial peptide.[13] Vitamin D receptors (VDR) are found ubiquitously in the body and there is much research ongoing into their various roles. Reduction to the pulmonary barrier integrity and increased lung permeability may be consequences of deletion of these receptors.[14] Higher status has been linked with lower levels of pro-inflammatory cytokines, while lower status may contribute to the activation of inflammatory processes.[15]

Evidence exists to support vitamin D supplementation in combatting respiratory tract infections, especially for those with lower baselines,[16] as well as tuberculosis[17] and chronic obstructive pulmonary disease.[18] This may be especially relevant when considering that NDNS data from 2008-2017,[19] which shows that 19% of young children (4-10 years), 37% of children (11-18 years), 29% of adults (18-64) and 27% of older adults (65+ years) were considered vitamin D deficient based on the Scientific Advisory Committee on Nutrition (SACN) recommendation of 25 nmol/L.

Zinc

Zinc has no specific storage mechanism meaning that low intakes can lead to rapid deficiency which is correlated with impaired immune function.[20] It plays a role in innate immunity, adaptive immunity and the production of cytokines. In a deficient state this can contribute to both oxidative stress and inflammation.[21, 22] Susceptibility to and fatality rates of sepsis are both higher in those with low zinc status.[23] Higher status has been shown to result in lower pneumonia incidence and better outcomes in the institutionalised elderly.[24] Supplementation may improve immune function and reduce infection incidence in otherwise healthy elderly populations.[21]

Food Sources *(Based on USDA 2019)*	Key Nutrients	Importance
Broccoli, spinach, kale, dairy, fish, eggs	Vitamin A (retinol)	Role in the regulation of innate and cell-mediated immunity and humoral antibody responses (Alpert, 2017)
Oranges, peppers, onions, cabbage, green leafy vegetables (kale, spinach), sprouts, citrus fruits, mango, strawberries	Vitamin C	Dose of > 200 mg/d supports reduction in risk, severity and duration of upper and lower respiratory tract infections. Requirements for vitamin C increase during infection (Carr & Magini, 2017)
Fish (salmon), dairy products (milk, cheese), red meat. *supplement of 10ug is required as the average British diet amounts to only 2-5ug of vitamin D	Vitamin D	Daily supplementation of vitamin D reduces the risk of upper respiratory tract infections (BMJ, 2017)
Vegetable oils (wheat germ, sunflower and safflower), nuts (peanuts, hazelnuts, almonds), sunflower seeds, green vegetables (spinach and broccoli), fortified foods (breakfast cereals, fruit juices, margarines, spreads)	Vitamin E	Vitamin E is a potent antioxidant and has an ability to modulate host immune functions (Moriguchi & Muraga, 2000)
Beef liver/tenderloin fortified cereals, oats, plain fat free yoghurt, milk, mushrooms, almonds, cheese	Vitamin B2 (Riboflavin)	Riboflavin administration affects neutrophil migration but does not alter acquired immune responsiveness (Verdrengh & Tarkowski, 2005)
Chickpeas, meat (beef liver, chicken breast), fish (salmon, tuna) fortified cereals, potatoes, banana	Vitamin B6 (pyridoxine)	Vitamin B6 deficiency impairs lymphocyte maturation and growth and impairs antibody production, T-cell function, and reduction in the size of the thymus gland (Alpert, 2017)
Seafood (clams), meat (beef liver), oily fish (trout, salmon), fish (tuna, haddock), dairy (milk and yoghurt)	Vitamin B12 (cobalamin)	Responsible for cell division and cell growth hence plays an important role in immune function (Alpert, 2017)

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KEY EVENTS

- **1st - 5th NNEdPro Cambridge Summer School in Applied Human Nutrition** - September 2020
- **6th International Summit** - September 2020

In light of the ongoing COVID-19 outbreak, both events will be converted to online events only.

Selenium

Selenoproteins are vital cellular antioxidants.[25] Susceptibility and progression of viral infections may be increased in those with selenium deficiency.[26] Like many other micronutrients, selenium plays a part in the inflammatory response as well as in the production of cytokines.[27] In deficient individuals, supplementation can improve the immune response.[28]

In summary

This is far from an exhaustive list and is meant as a prompt to consider improving intakes of specific micronutrients in these unprecedented times. It is also not meant to suggest that COVID-19 can be prevented, treated or symptoms reduced with diet alone, but highlighting the importance of good nutritional status in the face of such an acute challenge. Whilst this article focuses on micronutrients it is also important to note, especially for higher risk groups such as older individuals, that adequate intake of both calories and protein will help prevent malnutrition which is often community acquired and is associated with globally poor clinical outcomes for those admitted to secondary care.[29] There is also steadily emerging evidence supporting the importance of exercise, sleep and mind-care in supporting a healthy immune system which needs to be considered alongside nutrition. As in all infections, there are particular 'at risk' populations, one such group being those over 70 for COVID-19. Those in any age group with underlying conditions that weaken the immune system may also be more susceptible to infection and adverse outcomes. It is important to be aware that these higher-risk groups may be more likely to have micronutrient deficiencies whilst also requiring particular attention to their nutritional status overall. Because in some cases, diet alone may not be enough to correct deficiencies, supplements may be indicated but of course they should never replace a healthy, balanced diet. For those working in the nutrition professions and/or healthcare, this is a time to pay extra attention to the nutritional status of service users, especially bearing in mind the prevalent pattern of micronutrient deficiencies across our communities.

Food Sources (Based on USDA 2019)	Key Nutrients	Importance
 Green vegetables (spinach, kale, broccoli), beans and legumes, oranges, whole grain, meat (poultry, pork, liver), shellfish	Vitamin B9 (folate)	Plays an important role in cell division, and cell production in blood forming organs and bone marrow (Alpert, 2017)
 Haem sources – red meat, liver and other organ meats; non-heam sources – spinach, legumes, quinoa	Iron	The role of iron in immunity is in immune cell proliferation and maturation, specifically lymphocytes, associated with generating responses to infection (Alpert, 2017)
 Shellfish (oysters, crab, lobster), pork chop, baked beans, fortified breakfast cereal, pumpkin seeds	Zinc	Marginal zinc deficiency can impact immunity. Those deficienct in zinc, particularly children, are prone to increased diarrheal and respiratory morbidity (Gammoh & Rink, 2017)
 Brazil nuts, fish (tuna, sardines), shellfish (prawns), meat (turkey, beef stack, chicken), egg, cottage cheese	Selenium	Influences the innate and acquired immune systems (Rayman, 2012)
 Almonds, spinach, cashews, cereal, beans (black beans, edamame)	Magnesium	Magnesium-dependent functions in the synthesis, release, and activity of cells of the immune system have been reported from in vivo and in vitro studies (Kubenam, 1994)
 Beef liver, shellfish (oysters, crab), potatoes, mushrooms (shiitake), cashews, sunflower seeds	Copper	The immune system requires copper to perform several of its functions (Alpert, 2017)

For more information on diet and COVID-19, please visit the NNEdPro dedicated microsite at this link: www.nnedpro.org.uk/post/combatting-covid-19

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