



A Review of the Role Micronutrient Status in the Elderly Plays in Their Immune Response to Viral Respiratory Infections and the Potential Compromising Effects Medications Might Cause

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ABSTRACT

The elderly are a growing proportion of the global population. They are more susceptible to non-communicable diseases and respiratory viral diseases like influenza and covid19, which may lead to increased levels of morbidity and mortality than those of a younger generation. It is also reported that co-morbidities, especially diabetes, hypertension and coronary heart disease contribute significantly to the prognosis with these types of infections. That the immune system operates in a less efficient way as an individual ages, is now well understood and likely contributes significantly to this situation. The role of certain micronutrients in maintaining a healthy immune system is well recognised and demonstrated to play an important role both in preventing and controlling infection. However, for a number of reasons many elderly individuals have a less than optimal intake of many of the micronutrients that support the immune system. This review examines the contributory roles an aging immune system, suboptimal intake of micronutrients, comorbidities and the impact of the intake of medications typically used to treat them can play in the outcome of viral respiratory infections. It identifies the need for supplementation, especially in the elderly to support the immune system.

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1. INTRODUCTION

Around the world today, there are some 686 million people over 60 years of age, representing 12% of the global population and within the over 65 group, the cohort of those aged over 80 is the fastest rising subset, expected to reach 20% in 2050 [1,2]. Whilst developments in healthcare have been responsible for this increase in lifespan, new challenges have arisen as a result of extended longevity that can negatively impact on the quality of life and the ability to optimally function, such as a rise in the number of cases of non-communicable diseases of age and increased susceptibility to infection.

The World Health Organisation considers 3 – 5 million cases of seasonal influenza result in severe illness requiring hospitalisation, worldwide, and this results in 290,000 – 650,000 deaths annually [3,4], with severe infections of the lower respiratory tract most commonly resulting in sepsis-related death in the years between 1990 and 2017 [5]. Globally, acute respiratory tract infections, such as seasonal influenza epidemics, and more recently the coronavirus disease, COVID-19 outbreak are a major cause of morbidity and mortality. Hence, the development of public health practices to help reduce the impact of respiratory viruses and limit their spread, that include-avoiding those showing symptoms of infection, regular washing of the hands, social distancing and isolation, with vaccination wherever possible [6]. However, because influenza, like COVID-19, is an RNA virus, both are likely to evolve rapidly through high rates of mutation, which may allow escape of them from the neutralizing antibodies that pre-exist in the host [7].

There is a recognition that age-related diseases can be associated with an alteration of inflammatory and immune responses where the normally well-orchestrated, different types of processes and cells involved in defending the host against invading pathogens, become either diminished or dysregulated. This is typified on the one hand, by a level of hypoactivity, such as lowered T-cell mediated immunity, and hyperactivity, or on the other, through a chronic level of inflammation. However, as well as revealing the intrinsic, genetically determining processes associated with aging, recent studies have also highlighted the effect that modifiable factors associated around lifestyle can also play in this mosaic [8-10].

2. CHANGES IN IMMUNITY ASSOCIATED WITH AGING

It is this immune dysregulation that results in many people, although not all-aged 60–65 years or older-less capable of responding effectively to the challenges of allergens and pathogens to the immune system [11-13]. The effectiveness of long-term immune memory is also diminished, in a process commonly known as immunosenescence, which mainly appears to have an influence on adaptive immunity, but also affects innate immunity to a more limited degree [12]. Many cells of the immune system are renewed constantly, but as the systems responsible for their production reduce and become more mature as a result of aging, they are also less productive in their ability to produce immunity regulating T-lymphocytes. This reduction in the number of lymphocytes in the circulation coupled with their diminished ability to function effectively is characteristic of an older person's immune system [14,15]. Although immune memory can provide protection against numerous infections for many years and even decades, because of the increased lifespan described above, the reservoir of specific types of immune cells with specific memories may reduce over time, resulting in the elderly becoming more susceptible to infections [15-17]. As the long-term immune memory becomes weakened, there can also be a diminished response to vaccination [16].

These factors make it more likely that the elderly will experience prolonged infections and more severe symptoms, with a higher degree of secondary complications [18]. Approximately, two-thirds of these more elderly patients develop lower respiratory illness as a result of the common cold, whilst they are between 2 and 10 times more likely to die of infection than people of a younger age. In 2015, it was estimated 1.27 million deaths were attributable to lower respiratory tract infections in those aged 70 or older [19].

Although, in most adults influenza is not a life-threatening illness [20], deaths associated with it occur more frequently in people of 65 years of age or older [3]. In these patients the increased morbidity and mortality occur as a result of the previously described immune response dysregulation, which causes them to become more susceptible to secondary bacterial

infections of the respiratory tract such as bacterial pneumonia and bronchitis [21,22] especially if there is also a viral infection [16]. This may also explain why older people have a more limited response to vaccines than those of a younger age [16,22]. However, influenza vaccination can reduce complications and severe illness in those people aged 65 years or older, and should therefore continue to be used in this age group as well as other populations considered to be vulnerable [3].

3. THE ROLE OF MICRONUTRIENTS IN IMMUNITY

Micronutrients such as vitamins A, D, E, B6, B12, C, and folate, iron, selenium, copper, magnesium and zinc play complementary and important roles in supporting the adaptive and innate immune systems. A suboptimal or deficient intake of these micronutrients can negatively influence immune system functioning and decrease resistance to infections [23-25]. Such is the importance of optimal intake of the above micronutrients in supporting the immune system, that in the European Union, each of the above-with the exception of magnesium and vitamin E-has been granted an individual health claim to this effect [26] and their roles are well established in the literature [23,25].

In terms of enhancing innate immunity, these micronutrients collectively support the maintenance and development of physical barriers; growth, differentiation and motility/chemotaxis of innate cells; production and activity of antimicrobial proteins; killing and phagocytic actions of macrophages and neutrophils; and initiation and subsequent repair of inflammation. They promote adaptive immunity, via cytokine production; lymphocyte proliferation, differentiation, and homing; as well as the generation of memory cells and antibody production.

The detailed role of each of the above in the functioning of the immune system is beyond the scope of this review, but the following examples serve to demonstrate their contribution. Vitamin C has roles in several facets of immune health, including-supporting growth and function of both innate and adaptive immune cells; sustaining function of epithelial barriers, involvement in migration of white blood cells to sites of infection, microbial killing and phagocytosis, and production of antibodies [23]. Many cells of the immune system have vitamin D receptors and

hence it plays an important role in immunity. Vitamin D modulates inflammatory cytokine production, is involved in the promotion and differentiation of monocytes to macrophages as well as enhancing their effectiveness; and supports their presentation to antigens. In addition, metabolites of vitamin D play a role in the regulation of antimicrobial proteins with specific pathogen killing capacities, and hence help limit infections including those of the respiratory tract [27,28].

There is a two-way interaction between nutrition on the one hand and immunity and infection on the other. When nutrition is poor, the immune response is compromised, with a greater predisposition to infection, and an inadequate nutritional status may be further negatively impacted by the response of the immune system itself to infection, suggesting optimal immunity to an extent is dependent upon the nutritional status of the individual [29].

4. PHYSIOLOGICAL CHANGES AFFECTING THE NUTRITIONAL STATUS OF THE ELDERLY

Maintenance of homeostasis becomes more difficult with advanced age, especially under stress conditions [30,31]. A variety of changes occur at different areas in the gastrointestinal tract (GIT), including a reduction in production of saliva (xerostomy) and secretion of gastric acid, less absorption of micronutrients important for immunity (such as vitamin B12 and iron), slower motor function of the GIT resulting in slower food transit, and other alterations in digestion and nutrient absorption [32,33]. There also appears to be a trend towards a decrease food intake [34], which might be due to homeostatic factors as a result of a dysregulation in the secretion and response to hormones involved in food intake control such as ghrelin, cholecystokinin, or insulin [32]. These factors, together with changes in perception of taste and smell alter food preferences and appetite and affect food intake. Other factors, for example, low income, social isolation, illness, the use of several medications, lack of social support, limited quality of life, restricted mobility, or depression might also compromise food intake [35]. Also, problems with dentition and dental hygiene or xerostomy can affect food choices and dietary patterns. Fat mass can also change over time, as typically bone mass and lean mass decrease which can result in sarcopenia [36]. Similarly, plasma concentration of albumin typically decreases as

does the total body water content [37]. The food choices of many older people also tend to be different possibly through the selection of cheaper items which might be less nutrient dense or simply eat less, or perhaps because they live in a care home which provides only meals that are most suitable for the more frail members of their community, or have health conditions of a chronic nature that might in certain cases require hospitalization [38,39].

5. THE TYPICAL MICRONUTRIENT STATUS OF OLDER PEOPLE COMPROMISES IMMUNE FUNCTION

Although for older people, the official dietary allowances that are recommended, suggest their energy needs are less than for those of a younger age, their requirements for micronutrients are generally the same [40]. However, deficiencies in these micronutrients are not uncommon and it has been estimated in those aged 50 or above that 35% of this population in USA, Europe and Canada are demonstrably deficient in at least one, and often more micronutrients [41]. In the United States, for example, intakes below recommendations are common for most of the immune supporting micronutrients listed earlier, but particularly vitamins A, C, D, and E, selenium, magnesium and zinc. Vitamin B6 intake is low in the elderly, and folate, iron and copper intake are often below recommendations in females [42-44].

In Europe, intakes of vitamins D, E, folate and selenium are low in all age groups, with other micronutrients including vitamin C also below recommendations in specific age groups [45]. In Europe too, in people who are older, data suggest there to be an inadequate intake of almost all micronutrients, especially vitamin E and folate in males and females and vitamin D in the latter. Older females appear at the highest risk of deficiency, especially for vitamins A, C, D, B12, zinc and iron [46]. In China, inadequacies in both intake and status of the immune-supporting micronutrients are also quite common, including for vitamins A, D, E and C, folate, zinc, selenium, iron and magnesium [47-49].

In both free living older people and those in long-term care facilities, an inadequate intake of vitamins A, B12, D, E and zinc has been reported, whilst reduced food intake is suggested to result in lower levels of zinc, iron calcium, vitamin E and B vitamins [50].

6. CONSIDERATIONS AROUND SUPPLEMENTATION FOR THE ELDERLY

In order to attenuate the levels of oxidative stress which plays a significant role in immune dysregulation in the elderly, an adequate supply of micronutrients with antioxidant activity (e.g., vitamin C, zinc and selenium) is needed. However, in older people the ability to produce antioxidants in the body is less effective [51]. The skin of adults aged over 65, also synthesises vitamin D at a rate 75% more slowly compared to younger adults [52]. A suboptimal intake of micronutrients can affect the functioning of various components of the immune system, resulting in lowered resistance to infections and increases in the severity of symptoms. Multiple micronutrient deficiencies in older people can impair immunity, with the result that increases in the frequency and severity of common infections of both the upper and lower respiratory tract are experienced [13,53].

For example, zinc deficiency can result in reduced numbers and activity of lymphocytes, together with an increase in oxidative stress and inflammation, with the result that risk for all infection types (viral, fungal and bacterial) is elevated [54,55]. In older people, a marginal deficiency of zinc is frequently reported, as generally their dietary consumption is reduced and possibly due to impairments in absorption and cellular uptake, concentrations of zinc in plasma also decline [56]. In older healthy people, zinc supplementation at both low and moderate doses has been demonstrated to help increase both numbers and potency of immune cells, resulting in benefits in immunity that helped lower the frequency and morbidity of pneumonia, the common cold, influenza and cold sores [57].

Increased susceptibility to infections is also a risk when vitamin C status is low, as is a more limited ability to counteract oxidative stress from reactive species such as free radicals released as a part of the response to pathogens, which can decrease levels of the vitamin even further [58]. Older people, especially females are at risk of deficiency of vitamin C [59] and adequate intakes are required to optimize levels in tissues and cells and to help provide protection against systemic as well as respiratory infections, whilst during infection higher levels are needed to counterbalance the increased metabolic demand caused by inflammatory responses to the pathogen [23].

Supplementing vitamins A, C and E in elderly people resulted in an enhanced proliferative response of lymphocytes to infections and elevated numbers of immune cells, whilst with higher levels of vitamins C and E, increases in immune cell activity together with an enhanced response to influenza virus vaccines, which can reduce the number of days of infection has been observed [60]. In nursing home residents supplemented with vitamin E, the risk of infections of the upper respiratory tract, most typically the common cold, was significantly lower, although no apparent effect was reported on infections of the lower respiratory tract [61].

In older people, administration of a formulation containing a complex of micronutrients resulted in an increase in the populations of various types of cells involved in the immune system, which may reduce antibiotic usage, and result in improved responses post-vaccination [13,62]. Hence, the use of supplements with adequate doses of a various micronutrients can deliver benefits.

As already highlighted, inflammation is an important element in the immune response which is the result of the production of pro-inflammatory mediators. These compounds are released from a number of cells of different types and result in fluid influx, along with other mediators and cells of the immune system that together work to control an infection. At the end of the immune response, the resolution of inflammation typically occurs relatively quickly as the result of the activation of specific negative-feedback mechanisms. These include enzymatic conversion of mediators that resolve inflammation, such as protectins, resolvins, and maresins which are derived from the omega-3 fatty acids EPA and DHA present at the site of infection. Together with other molecules, these compounds orchestrate the resolution of inflammation and support healing at the site of the process, which can include the respiratory tract [63,64]. A suboptimal delay in resolution of inflammation might be the result of a deficiency in these Omega 3 fatty acids [64].

Co enzyme Q10 (CoQ10) is an important mitochondrial redox component that plays a pivotal role in cellular energy production. It is present in all biological membranes, but predominantly in the phospholipid membrane of the mitochondria, where it acts to stabilize the membrane. This compound is a potent

intracellular free radical scavenger and is the only lipid-soluble antioxidant endogenously synthesized in humans [65,66]. However, this production begins to progressively decrease after the age of 20 [67], so that the ability to synthesize CoQ10 from food decreases with age, resulting in reduced serum levels [68]. Poor eating habits, stress, infections, and also some drugs, may further reduce serum levels of CoQ10 [69-71].

The effect that a combination of depleted levels micronutrients and oxidative stress induced by influenza produces has lead a number of investigators to examine those dietary components that have known antioxidant activity as likely therapeutic adjuncts to attenuate the pathogenesis of influenza [72-74]. It is also known that any dysregulation of the inflammatory response that is induced by an influenza virus, commonly known as the "cytokine storm," can significantly contribute to morbidity and mortality associated with the infection [75-77]. A meta-analysis of clinical trials on supplementation of CoQ10 identifies its ability to moderate an inflammatory response [78]. In those chronic conditions where an over-activity and overproduction of pro-inflammatory cytokines are typical, administration of CoQ10 led to an attenuation of markers of inflammation and down regulation of pathways associated with pro-inflammatory signalling. A recent study of patients with acute influenza analysed their serum CoQ10 concentrations over 3 influenza seasons and compared them with controls [79]. Overall, acute influenza patients had levels of CoQ10 that were lower than controls.

Given the importance of micronutrients in maintaining a healthy immune response and considering numerous individuals of all ages have deficiencies in one or more of those that cause detrimental effects on this process, there would appear to be a sound arguments for adequate supplementation to support immune function and maintenance, including after an infection.

7. NUTRITION AND THE GUT MICROBIOME IN THE ELDERLY

Changes related to age that affect the gut microbiome are associated with an accompanying downturn in the normal immune system function that together may cause an elevated risk of frailty and infection [80-82]. Typically, in elderly individuals the gut microbiota

is characterized by changes in the dominant species, a reduced bacterial diversity, an increase of facultative anaerobic bacteria, a decline in beneficial microorganisms, and a difference in the production of bacterial metabolites. Short chain fatty acids (SCFA) are the main metabolic products produced by bacteria in the colon and levels are reduced in elderly, with differences in their ratios compared to healthy younger adults [81,83]. It is thought the changes in various metabolites may be related to the shifts toward a metabolism in the elderly that is predominantly putrefactive and away from one that is normally and predominantly saccharolytic in younger adults [84].

However, it is important to recognise that these changes may not necessarily result in a detrimental effect to health, since within the gut microbiota, some functional redundancy does exist and hence not all compositional modifications will be manifested as a functional inadequacy. Nevertheless, generally an altered microbiota in the elderly has been frequently reported to be associated with frailty [80,85] and such changes in gut microbiota in the elderly may influence host physiological functions, including immunity [86]. It is possible that immunosenescence could be the result of an abnormal response by the immune system that has been activated by the gut microbiota, which may be due to age related modifications in the gut microbiome or diminished mucosal tolerance, or both [87]. Studies have shown supplementation with dietary probiotics has resulted in improved responsiveness of systemic immunity [88] and hence immunosenescence and alterations in the gut microflora could be inter-related and might affect health concurrently.

Studies suggest ageing could negatively alter levels of *Bifidobacteria* and *Lactobacillus*. In one study, the richness of the microbiota was reported to decrease in the group of elderly participants [89]. Reports have also suggested that the loss of diversity and richness in gut microflora is associated with greater frailty, that could be the result of an accumulation of medical conditions together with an unbalanced intestinal ecosystem which results on greater challenges to the immune system and hence higher susceptibility to pathogenic organisms [90]. Therefore, these findings together suggest that the decrease in gut microbial diversity observed in aging could also occur concurrently with a

dysregulation of the immune system in the host. Hence, the immune status of the elderly may be associated with the changes in gut microbiota and contribute or cause some age associated conditions and disorders.

8. VIRAL RESPIRATORY INFECTIONS AND COMORBIDITIES

Given the increased likelihood for the elderly to experience a higher burden of non-communicable diseases as they age, it is not surprising that the nature of these conditions might affect morbidity and mortality as a result of contracting a viral respiratory infection. Hence a retrospective study of patients admitted during the influenza season 2015-2016 suggests comorbidities that were observed with the highest frequency among the <65-years and 65-years-and-older age groups, were hypertension and diabetes [91].

It does indeed appear that diabetes contributes to an increase in the likelihood of flu-related illness that is more severe. One cohort study of 166,715 participants found that compared with those without diabetes, those with the condition are at a significantly increased risk of influenza related, serious illness, which underlines the relevance of vaccination in these patients. After taking into consideration possible confounders such as sex, age, location of residence, comorbidities, vaccination and socioeconomic status, there was a significant rise in all-cause hospitalizations associated with influenza in diabetic patients ($p=0.044$) [92,93].

Diabetes also seems to be an important comorbidity associated with prognosis in the novel coronavirus disease 2019 (COVID-19) where a recent study of non-survivors identified 22% of this cohort had diabetes [94]. Similarly, in a further study of those experiencing severe symptoms 24% had hypertension, 16% diabetes mellitus and 6% coronary heart diseases [95]. In another study, of hospitalised patients with COVID-19, 30% had hypertension and 12% were diabetic [96].

A recent meta-analysis and systematic review of 8 studies examined the prevalence of comorbidities in patients with this infection and included 46248 patients [97]. The most frequent were hypertension (17%) and diabetes (8%).

9. AGEING, MEDICATION AND POTENTIAL COMPROMISES IN THE ELDERLY

As noted above, the elderly and especially those with co-morbidities such as hypertension and diabetes appear to be more vulnerable to the severe effects of communicable respiratory disease such as influenza and COVID 19. However, often conditions such as hypertension and type 2 diabetes are present together as comorbidities. Indeed Age UK, estimates that in UK, 87% of those aged 85-100 with diabetes also suffer from hypertension, as do 77% of 60-84 year olds [98]. However, it is likely that these individuals will be receiving more than one medication to control these conditions. Typically these will be metformin as the first line treatment for diabetes, and one or a combination of drugs such as ACE inhibitors, Angiotensin II receptor agonists, calcium blockers and thiazide diuretics to control their hypertension and possibly statins as well to manage cholesterol levels. It is also estimated that around 50% of patients receiving metformin are co-prescribed acid controlling medications to control gastric reflux [99]. This type of situation is reflected in the fact that 50% of UK individuals aged 60-80 are taking at least 3 medications and 80% of those aged 80+ are using more than 3 prescription medications each day [100].

There is evidence that many of the above medications can impact upon the nutritional status of those taking them, especially micronutrients involved in maintaining and enhancing immune status as well that certain of these medications also detrimentally affect the microbiome and these impacts are discussed below.

As noted above the most common comorbidities in patients diagnosed with COVID-19, are frequently likely to be prescribed angiotensin-converting enzyme (ACE) inhibitors, which it is hypothesised may also have a direct influence on the progression of the disease. This is because it is known that human pathogenic coronaviruses use angiotensin-converting enzyme 2 (ACE2) expressed by cells in the epithelium of the lung, blood vessels, kidney and intestine to bind to their target cells [101]. In both, type 1 and type 2 diabetic patients, as well as those with hypertension treated with angiotensin II type-I receptor blockers (ARBs) and ACE inhibitors, it has been observed that the expression of the ACE2 enzyme is significantly increased.

Ibuprofen and thiazolidinediones have been noted to exert a similar effect [102]. Given that in diabetic patients ACE2 expression is increased and these individuals are often treated with ACE inhibitors and ARBs that also increase expression of the enzyme, along with the observation that the increased expression of ACE2 could facilitate infection with the virus, it could be hypothesised that this combination of factors could increase the risk of a poorer prognosis.

10. MEDICATIONS AFFECTING MICRONUTRIENTS INVOLVED IN IMMUNE REGULATION

10.1 ACE Inhibitors

ACE inhibitor use in a cohort of elderly patients resulted lower levels of 25-hydroxyvitamin D (25(OH)D) in serum compared to those not using the medication [103]. This was confirmed in two cross-sectional studies [104,105], whilst in two quasi-experimental investigations [106,107] no relationship was shown.

Data suggest a chelation of zinc by sulfhydryl moieties in captopril increases urinary zinc excretion [108-112]. Whilst links have been observed between low levels of zinc and captopril use and a loss of taste-reversed by the use of zinc containing supplements- this has not been confirmed in all studies [113,114]. Zinc loss appears to be greater with higher doses of captopril and longer duration of usage.

10.2 B-blockers

Propranolol has been demonstrated to depress CoQ10-enzymes of the myocardium. Metoprolol inhibited these enzymes less, and timolol's effect was negligible [115].

10.3 Calcium Channel Blockers

In a cohort study of elderly individuals, the use of calcium-channel blockers resulted in a reduction of 7.7 nmol/l in levels of 25(OH)D in the serum compared with non-use [116]. As calcium channel blockers such as diltiazem and verapamil are known to inhibit CYP3A4, the production of 25(OH)D precursors in the skin as a result of exposure to UV radiation may be decreased as a consequence, producing lower serum 25(OH)D [117-119]. It also appears that drugs, such as nifedipine, which are ligands for

the nuclear pregnane X receptor (PXR) can induce an increased catabolism of vitamin D [120].

10.4 Digoxin

Digoxin has been shown to decrease renal tubular reabsorption of magnesium, thereby increasing urinary excretion [121,122]. Given that patients prescribed digoxin for heart failure could also be prescribed thiazide or loop diuretics, there is increased risk of hypomagnesaemia [123].

10.5 Diuretics

In patients experiencing chronic renal failure, acute use of furosemide has been shown to increase urinary excretion of pyridoxine [124,125]. However, the relevance in hypertensive patients who have been treated with oral furosemide for several years is questioned [126].

Urinary excretion of vitamin C has been observed to increase after use of furosemide in chronic renal failure [124,125]. The authors recommended future monitoring of plasma vitamin C in these types of patients prescribed high doses of the drug as part of long-term therapy.

Van Orstein-Luiten et al reported an inverse association with these drugs and vitamin D in the elderly [127], but one other cross-sectional study in patients of a similar demographic failed to support this observation [103].

Data suggests the mean red blood cell concentration of folate in patients taking diuretics was significantly lower than that of patients not prescribed these drugs, and the authors also observed chronic use to be linked with a significantly higher serum homocysteine concentration, likely due to the decrease in folate levels [126].

Loop diuretics, impede renal reabsorption of magnesium which increases losses in the urine and lowers magnesium levels in serum. This appears to be the case with thiazide diuretics, as well, but to a lesser extent [128-133]. Some authors recommend that heart failure patients treated with loop diuretics should also receive electrolyte replacements [131]. Furosemide has also been reported to inhibit passive magnesium

uptake and increase renal magnesium excretion [134].

Thiazide diuretics have been reported to increase urinary zinc excretion by 50% to 60%, which appears to be sustained during chronic treatment [135-140]. It is therefore likely that prolonged therapy with thiazides might deplete zinc levels in tissues and possibly contribute to the impotence sometimes observed in patients using them chronically. A zinc-sparing diuretic such as Amiloride is a suitable alternative to thiazides to reverse this side effect.

One study suggests Thiazide diuretics inhibit CoQ10 enzymes NADH-oxidase and succinoxidase which are involved in mitochondrial energy production in the heart [141].

10.6 H2 Blocker

Retrospective study of over 1050 elderly patients observed that initiation of cobalamin therapy was significantly associated with regular use of histamine-2 blockers (H2RAs) over a 5 year period compared to baseline. This correlation was robust after adjusting for gender, age and institutional residence [142].

In a retrospective study spanning the period from January 1997 and June 2011, Lam et al. assessed patients having a diagnosis of vitamin B12 deficiency and compared levels in those without a deficiency [143]. A use of H2RAs for two years or more was associated significantly with a greater risk of deficiency of vitamin B12. Current and previous use of inhibitors of gastric acid was associated significantly with vitamin B12 deficiency, especially if used long term and at higher doses [144].

Absorption of Folic acid in the small intestine is optimal at pH 5.5 to 6 [145] Given that H2 blockers increase this pH, they may therefore reduce folic acid absorption, which is likely to be of clinical significance in chronic H2RA or antacid usage especially in those consuming foods low in folic acid [146,147].

Preclinical studies demonstrate cimetidine inhibits CYP enzymes [148,149]. A small study of patients taking cimetidine for gastric ulcers, identified no significant change in concentrations of 25(OH)D in serum during treatment, but there was a significant rise once this medication was discontinued [150]. In contrast, in preclinical

models, ranitidine has not been shown to inhibit the same CYP enzymes [151].

One study has demonstrated a close correlation between the capacity of gastric juice to release iron from food iron and its subsequent absorption [152]. Both in controls and in those with hepatic hemochromatosis, the reduction in acid secretion as a consequence of taking cimetidine resulted in a significant lowering of non-heme iron absorption [153].

10.7 Metformin

Metformin has been shown to with reduce levels of folate, which resulted in an increase in homocysteine (Hyc) in a placebo-controlled, randomised trial over 16 weeks, in participants with T2DM [154]. Another trial examining the effects of metformin usage in patients with T2DM arrived at the same conclusion regarding metformin and folate status [155]. Hyperhomocysteinemia that has been shown to be evident in some diabetic patients, can further contribute to their already elevated risk of cardiovascular disease, and whilst this has been attributed to reduced vitamin B12 levels, it has also to a lesser extent, been suggested to be due to lower folate concentrations which are also observed in the condition [156-159].

Metformin has been demonstrated to impair vitamin B₁₂ absorption, and serum levels of the vitamin have been inversely correlated to both the length of administration of the drug and the dose used [160-163]. In patients with T2DM, the suggested mechanisms that result in this vitamin B₁₂ deficiency include: changes in small bowel motility that might stimulate bacterial overgrowth; alterations in levels of intrinsic factor (IF) that result in inactivation of vitamin B₁₂ absorption, or competitive inhibition of the process, and interplay with cubulin endocytic receptors. It has also been demonstrated that metformin inhibits calcium-dependent absorption of the vitamin B₁₂-IF complex at the terminal ileum [164].

The literature suggests that anything from 10–30% of those prescribed prolonged metformin therapy experience malabsorption of vitamin B₁₂, with 6–9% of patients developing a deficiency [165]. Risk factors associated with this phenomenon include, higher metformin dose, vegetarian diet, older age, and 3 years or more use of metformin. One significant study demonstrated that as little as 16 weeks of use of metformin resulted in diabetic patients having

lower vitamin B₁₂ concentrations in comparison to participants not receiving this drug, or non-diabetics [166]. Liu et al compared vitamin B₁₂ deficiency incidence in elderly diabetic patients prescribed metformin with those who were not receiving the medication and concluded a significantly association existed between use of the drug and deficiency of vitamin B₁₂ [167]. The authors recommended physicians assess baseline vitamin B₁₂ status in patients prescribed metformin, and subsequently monitor the nutritional status of these patients, and where necessary recommend a supplement containing vitamin B12 as appropriate.

In a cohort study, mean 25(OH)D serum levels of patients prescribed oral antidiabetics was reported to be 7.3 nmol/l lower in comparison to controls [103]. The authors of a separate cross-sectional study suggest that any lowering effect of metformin on vitamin D levels might have been masked by use of supplements at the time of diagnosis [129]. But, in a study of Dutch community dwelling geriatric out patients, after adjustment for gender and age, statistically significant negative associations were found for use of metformin and vitamin D status, with those not using vitamin D supplements and prescribed metformin having levels of the vitamin 14.4% lower compared to controls [168].

11. PROTON PUMP INHIBITORS

A study, with a small number of patients, assessed the impact of proton-pump inhibitors (PPIs) on proton-coupled folate transporter (*PCFT*) expression in biopsies. In some subjects treated with PPIs, there was a significant reduction (~40%) in *PCFT* expression. [169]. At a microbiome population level, the effects of PPIs are more prominent than those of antibiotics or other frequently prescribed medications in terms of decreasing diversity which may also impact upon the availability of folate from this source [170].

Effective absorption of Vitamin B12 from food requires it to be cleaved from dietary proteins by peptic enzymes, primarily pepsin, which in turn uses gastric acid to release it from its precursor, pepsinogen. Without this process vitamin B12 would be unable to bind to R-proteins, that are necessary for the next phase of vitamin B12 absorption in the duodenum where pancreatic enzymes separate this complex to permit binding of cobalamin to intrinsic factor (IF) [171]. This IF-cobalamin complex is then absorbed in the

ileum. Hence conditions such as achlorhydria and atrophic gastritis can result in malabsorption of vitamin B12 and its possible subsequent deficiency [172].

In a study of male patients, it was reported that those receiving short term omeprazole treatment given a 20mg dose experienced a 66% reduction of absorption of cyanocobalamin at the end of treatment, whilst patients receiving a 40mg dose experienced a reduction of 88% [173]. It has been suggested in a systematic review that Proton Pump Inhibitors diminish the protein-bound vitamin B12 absorption whilst not entirely inhibiting it [174].

A two year study with almost 26,000 participants examined the effect of consumption of PPIs in patients who also experienced concomitant vitamin B12 deficiency and identified a dose dependent effect on the status of the vitamin, with the odds of developing a deficiency, 65% higher in those taking the medication for the duration of the study or longer compared to treatment naive individuals [175].

A systematic review of the subject identified [176] an association between the chronic use of drugs that suppress gastric acid production, especially PPIs, with the incidence of lower levels of B12, and that in the elderly a deficiency in iron was more frequently manifested. However, it seems PPIs can limit absorption of vitamin B 12 in its' dietary, protein-bound vitamin form, but not in that of supplements [177-179].

It is hypothesised that hypochlorhydria might result in malabsorption of calcium and that chronic use of acid suppressant medications could be a clinical risk factor in osteoporosis leading one group to suggest long term treatment with PPIs at high doses in elderly patients might require supplements of vitamin D and calcium [180-182].

In a study in patients with hemochromatosis examining the effects on iron absorption as a result of PPI usage, the medication was shown to reduce non-heme iron absorption by around 50% [183]. PPI therapy has also been shown to reduce the annual volume of blood required to be venesected from 2.5l prior to treatment to 0.5l subsequent to therapy. However, in normal circumstances there have been no reports of iron deficiency linked to PPI medications, but there may be grounds for monitoring the status of those with chronic anaemia.

The negative effect of PPIs on magnesium status is considered to be a class effect, with numerous studies suggesting long term treatment to be associated with an elevated risk of hypomagnesemia [184-195] through an inhibition in the intestine of active transport of magnesium. Indeed, almost a decade ago the FDA issued a warning that PPI use for longer than one year may induce hypomagnesemia [186]. In a cross-sectional study in hospitalised patients, aged over 50, receiving PPI therapy, Gau et al identified [196] that use at doses routinely recommended as well as those prescribed at higher levels was likely to increase the risk of hypomagnesemia, which might result in a subclinical deficiency status even in asymptomatic patients.

A 2012 study assessed the effect that omeprazole usage might have on levels of the trace elements, iron, phosphorus, calcium, copper and zinc in serum [197]. Only zinc status in males was found to be significantly affected.

11.1 Statins

Statins exert their cholesterol lowering effects by inhibiting the hydroxymethylglutaryl-CoA reductase (HMG Co-A reductase) enzyme which is rate-limiting in cholesterol synthesis [198]. Since, cholesterol is a precursor of vitamin D, it is thought that statins might also reduce synthesis of this vitamin [199,200]. Furthermore as simvastatin, lovastatin and atorvastatin are primarily metabolized by CYP3A4, competition for this enzyme might also present another route for drug/vitamin interactions [201,202]. In contrast CYP2C9 primarily metabolises rosuvastatin and fluvastatin, whereas pravastatin and pitavastatin are degraded in the stomach and so interact in a minimal way with hepatic enzymes [200,203]. It is speculated that a deficiency of vitamin D might be associated with myopathy and hence cause a higher incidence of statin intolerance [204], exemplified by one study in hypercholesterolemic patients which identified low serum vitamin D levels in those experiencing statin intolerance as a result of myalgia [205]. These patients were restarted on a statin and placed on vitamin D supplementation over a median period of time of 8 months after which time 87% were myalgia free and seemed to be tolerant of re-initiation of statin treatment.

Three studies have reported treatment with atorvastatin, pravastatin and simvastatin to be associated with a significant lowering of vitamin

E in plasma [206-208]. This was confirmed by a more recent study, however, this group found that the total cholesterol/vitamin E ratio not to be significantly altered in patients using atorvastatin [209].

Whilst fibrates have been observed to elevate plasma selenium levels in dyslipidemic patients, statins appear to induce the reverse effect [210]. It has been suggested that statins may cause this by inhibition of selenocysteine tRNA [211-213]. This selenoenzyme has been reported to regenerate ubiquinol-10 and hence the depletion of CoQ10 by statins may be another explanation [214, 215].

One study has demonstrated that statin therapy can lower serum levels of zinc in dyslipaemic patients [216].

Primary deficiency of Co Q10 is well understood and is known to be the result of gene mutations involved in its Biosynthesis. However, a secondary deficiency may be linked to the use of statins which inhibit hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase in order to treat hypercholesterolemia [217]. These drugs also block the synthesis of mevalonic acid, which is a precursor of coenzyme Q-10 through the same mechanism of action [218,219]. Hence evidence demonstrates statins can exert a negative effect on serum levels of coenzyme Q-10 levels and studies show statin therapy generally lowers serum CoQ10 levels, which may be both dose related as well as statin specific [220-227]. This is verified where one study reported a 40% reduction in Coq10 levels over 3 months in healthy individuals treated with 20mg per day of either pravastatin or simvastatin, whilst another in healthy people taking 10mg of atorvastatin daily or 20mg per day of pravastatin did not observe significant decreases in CoQ10 levels, although a higher dose of 80mg per day of atorvastatin administered subsequently for 30 days did result in a 52% reduction in CoQ10 levels [228,229]. In a different study those taking simvastatin 20 mg/day for 4 weeks experienced reduced serum coenzyme Q-10 levels of about 32%, whilst levels in muscle actually increased by up to 47% [230].

It has been shown, including in a randomised clinical trial in coronary heart disease patients, that statins can elevate levels of arachidonic acid, the primary omega 6 fatty acid component of cell membranes [231,232]. Because this class of fatty acids competes through a number of

pathways affecting the progression and prognosis of cardiovascular disease, this could also consequently attenuate the potential protective contribution of Omega 3 fatty acids [232-240]. Omega 3 fatty acids have been demonstrated to confer greater protection in this respect when concentrations of Omega 6 fatty acids are reduced [241,242]. Thus statins may inhibit Omega 3 metabolism by disrupting the Omega 3/6 ratio and interplay and favour the Omega 6 pathway.

12. VITAMIN K ANTAGONISTS

In patients using vitamin K antagonists, lower 25(OH)D levels have been reported in two cross-sectional studies [103,127] as well as in a similar cross-sectional study of males [243]. However, other smaller studies have not reported this effect [244-247].

13. MEDICATIONS AFFECTING THE MICROBIOME

The recommended oral daily doses of metformin typically range between 1 and 2 g per day. Hence, given the reported bioavailability of the drug is around 50%-60%, there is still a level of faecal recovery of 20%-30%, suggesting a significant proportion remains available to interact with GI microbiota [248]. Given that glycerophosphate dehydrogenase is known to be inhibited by metformin, this activity could affect many commensal microbiota, such as *Bacillus subtilis* which utilise this enzyme, thereby resulting in d-lactate overproduction in the colon [249]. Other organisms that utilize colonic sugars, such as *Lactobacillus*, *Bifidobacterium* and *Eubacterium* species might also contribute to d-lactate overproduction [250] and other colon microbiota can also convert d-lactate to l-lactate, thereby contributing to the plasma lactate pool [251]. Additionally, unabsorbed glucose or glucose polymers that appear in the colon provide a substrate for lactate-producing bacteria [252] which contribute to further elevated levels of both d- and l-lactic acid that can be absorbed into the circulation. Hence it is probable that the accumulation of lactic acid in the colon might result in some, or most, of the GI side effects of metformin, particularly in users that consume foods high in sugars and starch [253]. Moreover, the GI predominant microbiome in type 2 diabetics appears to be rich in bacteria that harvest sugars [254].

Meta-analyses have shown increased incidence of *Clostridium difficile* infection is associated with PPI usage [255], as well as higher rates of recurrence of infection in patients who are hospitalised, and higher risks of community-acquired *Streptococcus pneumoniae* and other enteric infections [256-261]. In cirrhotic patients, a UK study observed an independent predictor of infection to be prescription of PPIs as well as reporting a significantly lower diversity in the gut microbiota compared to non-users [262]. Another study that combined an analysis of three data sets of PPI users and non-with users, identified a significant decrease in diversity and species richness metrics in the former compared to the latter group [263]. A further study found usage of PPIs to be significantly associated with architectural changes in gut microflora [264]. This was similarly reported in cirrhosis patients [265]. A trend of a decrease in diversity after both one week and one month of PPI treatment compared to treatment-naive individuals was also identified in patients infected with *C. difficile* [266].

PPIs are frequently prescribed to patients using NSAIDs to provide gastric protection, and this has led to observed cytotoxic effects in the small intestine [267] as a result of dysbiosis which has been corrected in preclinical studies by supplementation with microbiota enriched with *Bifidobacteria*. This suggests the combination of these medications may induce cytotoxicity in the small bowel through an effect mediated through the microbiome.

Side effects in the GI tract, such as constipation or diarrhoea, abdominal pain, and bloating as are commonly experienced with statin usage which suggests these drugs may induce alterations of the gut microbiome [268,269]. Since bile acids and statins share the same intestinal transporters, interactions between the two may be the cause of these problems. Preclinical models have suggested statins can affect bile acid metabolism and impact upon the expression of inflammatory markers that are recognised to influence the structure of the gut microbiota [270]. Data also suggest that statins might exert a direct activity of an antibacterial nature that could explain some of the changes in the gut microbiota [261-275].

14. CONCLUSION

It is clear from the above that a number of medications impact negatively upon

micronutrient status often affecting multiple vitamins and minerals. Given the previously discussed frequent occurrence of co-morbidities in the elderly these are likely to be treated via a number of combinations of medications. Table 1 indicates the potential additive impacts of combinations of medications frequently used to treat those common co-morbidities in this cohort which have been shown to negatively affect the prognosis of viral respiratory infections. With the exception of calcium channel blockers and vitamin K antagonists, every other type of medication listed impacts upon more than one component which supports a healthy immune system. It can be hypothesised that the higher the number of medications used that impact on one component, the greater the likelihood these additive negative effects will be to move from the possible or probable category into the probable and significant domains, respectively. This demonstrates the additive negative effects of multiple medications and highlights the need for additional supplementation in the elderly to support their micronutrient and immune status.

Optimal intake of all the nutrients is important in supporting a well-functioning immune system and would ideally be met by consumption of a diverse and well-balanced diet, but as identified above this can be difficult to achieve, especially in the elderly. Even populations in developed countries exhibit inadequate micronutrient intakes versus the Recommended Daily Allowances (RDA) [276,277]. It is also clear that optimal nutritional support for the immune system can require higher intakes of certain micronutrients, because simultaneously, infections and different stressors can lower micronutrient status. For example, vitamin C stores are diminished in periods of infection and in order to restore normal blood levels, increased intakes may be needed [23]. In addition to micronutrient inadequacies, omega-3 fatty acid (EPA + DHA) intake and status are also commonly below recommendations, including in the Americas, Europe, the Middle East, and parts of Asia including China [278,279].

That the nutritional status of many elderly relating to micronutrients which can support the immune system is suboptimal is clear from the above. It appears that existing comorbidities such as diabetes, hypertension and coronary heart disease can significantly affect the prognosis relating to viral respiratory infections. The fact that many of the medications used to treat these comorbidities can further negatively impact upon

Table 1. Medications impacting on nutritional components contributing to a healthy immune system (106-270)

	Vit B6	Folate	Vit B12	Vit C	Vit D	Vit E	Fe	Mg	Se	Zn	CoQ10	Omega 3 fatty acids	Microbiota
ACE inhibitors					?					x			
B blockers											x		
Calcium channel blockers					x								
Digoxin								x					
Diuretics	?	x		?	?			x		x	?		
H2 blockers		x	xx		?		?	x					
Metformin		x	xx		x								x
PPIs		x	xx		?		?	xx		x			x
Statins					?	x			x	x	x	x	x
Vitamin K antagonists					?								

Key- Possible negative impact on status; x-probable negative impact on status; xx-significant negative impact on status

the nutritional status of micronutrients that can support the immune system needs to be taken into serious consideration in these patients. Moreover, in individuals who are receiving multiple treatments for these common comorbidities there is a likely a significant negative additive effects on the status of these micronutrients will occur and which can further detrimentally affect the situation.

In these circumstances supplementation with a high quality multivitamin, providing at least 100% of the micronutrients proven to support the immune system, as well as coenzyme Q10, along with an omega 3 oil-rich in EPA and DHA, appears a prudent strategy for most people, but especially the elderly. For those on any of the medications discussed above, this is also a sensible recommendation, but especially so in those elderly with the co-morbidities of concern such as diabetes, hypertension and coronary heart disease and where multiple drugs are prescribed. In the elderly too the use of a probiotic might also be considered to correct any dysbiosis in the microflora.

This strategy has a number of appealing merits. In the first instance, in addition to a well-balanced diet, micronutrient, probiotic and omega-3 fatty acid supplementation where needed, is an effective, safe, and relatively low-cost approach to maintain optimal nutritional status and support immune function, and hence help prevent and lower the risk of infections and their consequences. Secondly, in the elderly, especially, it is worth considering higher levels of supplementation for vitamins C and D above the RDA recommendations. Meta-analyses have demonstrated supplementation with vitamin C delivers significant risk reductions as well as a reduced impact in infections of the respiratory tract in older patients, with possibly higher doses required in those who are chronically ill [280-283]. Similarly, meta-analyses suggest daily or weekly supplementation with vitamin D supplementation can lower the risk of respiratory tract infections in adults and children, however, this was not observed with infrequent bolus doses [284-289]. Next, an adequate intake, at a dose recommended by most expert bodies, of 250mg of EPA and DHA provides via the production of anti-inflammatory metabolites, delivers assistance in resolving inflammation as a result of infections such as those affecting the respiratory tract [290,291]. Finally, there is good evidence that probiotics can correct imbalances

in the microflora and boost the immune system, especially in the elderly [292-296].

The ongoing multifaceted strategy to control viral respiratory infections, especially those of a novel nature requires that the immune status of individuals is optimised to help control the impact of these pathogens. It is clear many people around the world, especially the elderly have an insufficient intake of those vitamins and minerals that can help optimise immune status, and given that significant numbers of individuals are taking medications that further impact upon the status of these micronutrients, adequate and appropriate nutritional supplementation appears an effective strategy to help limit the impact of seasonal and novel viral respiratory infections and to contribute to the improvement of public health.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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