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Essential sufficiency of zinc, ω-3 polyunsaturated fatty acids, vitamin D and magnesium for prevention and treatment of COVID-19, diabetes, cardiovascular diseases, lung diseases and cancer

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Essential sufficiency of zinc, ω-3 polyunsaturated fatty acids, vitamin D and magnesium for prevention and treatment of COVID-19, diabetes, cardiovascular diseases, lung diseases and cancer

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Abstract

Despite the development of a number of vaccines for COVID-19, there remains a need for prevention and treatment of the virus SARS-CoV-2 and the ensuing disease COVID-19. This report discusses the key elements of SARS-CoV-2 and COVID-19 that can be readily treated: viral entry, the immune system and inflammation, and the cytokine storm. It is shown that the essential nutrients zinc, ω-3 polyunsaturated fatty acids (PUFAs), vitamin D and magnesium provide the ideal combination for prevention and treatment of COVID-19: prevention of SARS-CoV-2 entry to host cells, prevention of proliferation of SARS-CoV-2, inhibition of excessive inflammation, improved control of the regulation of the immune system, inhibition of the cytokine storm, and reduction in the effects of acute respiratory distress syndrome (ARDS) and associated non-communicable diseases. It is emphasized that the non-communicable diseases associated with COVID-19 are inherently more prevalent in the elderly than the young, and that the maintenance of sufficiency of zinc, ω-3 PUFAs, vitamin D and magnesium is essential for the elderly to prevent the occurrence of non-communicable diseases such as diabetes, cardiovascular diseases, lung diseases and cancer. Annual checking of levels of these essential nutrients is recommended for those over 65 years of age, together with appropriate adjustments in their intake, with these services and supplies being at government cost. The cost:benefit ratio would be huge as the cost of the nutrients and the testing of their levels would be very small compared with the cost savings of specialists and hospitalization.

Keywords: zinc, ω-3 PUFAs, vitamin D, magnesium, essentiality, SARS-CoV-2, COVID-19, diabetes, cardiovascular diseases, lung diseases, cancer, supplementation

Abbreviations

1α,25(OH)$_2$D$_3$	1α,25-dihydroxyvitamin D$_3$, calcitriol	IL-x	interleukin x
25(OH)D	25-hydroxyvitamin D$_3$	IL-1RN	IL-1 receptor antagonist protein
ACE	angiotensin converting enzyme	IP-10	interferon-γ-inducible protein
ACE2	angiotensin converting enzyme 2	M1,2	macrophage type 1, (or 2)
ADAM17	disintegrin and metalloproteinase domain 17	MMP-2,9	matrix metallopeptidase 2, (or 9)
ALA	α-linolenic acid	NF-κB	nuclear factor κ-light-chain-enhancer of activated B cells
Ang	angiotensin	P38 MAPK	p38 mitogen-activated protein kinases
ARDS	acute respiratory distress syndrome	PDGF	platelet-derived growth factor
ATR1	AT1 receptor	PGE2	prostaglandin E$_2$
CCL2 (MCP-1)	monocyte chemotactic protein-1	PUFA	polyunsaturated fatty acid
CCL3 (MIP-1α)	macrophage inflammatory protein 1α	RANTES	regulated upon activation, normal T cell expressed and presumably secreted
c-Kit	stem cell factor receptor	RAS	renin-angiotensin system
CRP	C-reactive protein	ROS	reactive oxygen species
CYP27B1	1α-hydroxylase	SAA	serum amyloid A
DHA	docosahexaenoic acid	SCF	stem cell factor
EPA	eicosapentaenoic acid	TGF-β	transforming growth factor β
ERK1/2	extracellular signal-regulated kinase 1/2	Th	T helper
FGF	fibroblast growth factor	TLR	toll-like receptor
G-CSF	granulocyte colony-stimulating factor	TMPRSS2	transmembrane serine protease 2
GM-CSF	granulocyte-macrophage colony-stimulating factor	TNF-α	tumour necrosis factor α
HCQ	hydroxychloroquine	Treg	regulatory T cell
HIF-1α	hypoxia-inducible factor 1-α	VDR	vitamin D receptor
IFN-γ	interferon-γ	VEGF	vascular endothelial growth factor

1. Introduction

SARS-CoV is the original SARS that was virulent in the early 2000s; it is the virus that leads to the COVID-19 disease state. There is an immediate need for a prophylaxis and treatment for COVID-19. Even if the vaccines that are being distributed and further developed are successful in their efficacy and prevention of transference, there will always be a need for a prophylaxis and treatment for like viruses and comorbidities, particularly in poorer countries. It is therefore timely to present the advantages of the essential combination of zinc, ω-3 PUFAs, vitamin D and magnesium as these treatments are low in cost, extensive in their actions, and safe as they are naturally present in the human body.

The essential sufficiency of zinc, ω-3 PUFAs and vitamin D for prevention and treatment of cancers has been previously presented [1]. The prevention and treatment of COVID-19 and associated comorbidities is currently of the highest concern. Furthermore, the four principal non-communicable diseases that are

most prevalent world-wide are diabetes, cardiovascular diseases, lung diseases and cancer [2]. The comorbidities discussed here in the context of COVID-19 include these non-communicable diseases as well as ageing and obesity. Zinc, ω-3 PUFAs, vitamin D and magnesium, although very different in their modes of action, have many similar end-effects. The commonality of zinc, ω-3 PUFAs, vitamin D and magnesium in inhibiting inflammatory situations, as well as their ability to correct immune dysfunction, together with the low cost and safety of these nutrients, makes them ideal as front-line prevention measures and adjuvants in treating COVID-19 and associated comorbidities, as well as the principal non-communicable diseases in non-COVID situations.

Extensive literature searches were made in preparation of this manuscript. PubMed was principally used with a wide range of search strings. Separate searches were made for key concepts together with each of the individual components: ie, zinc; (PUFAs OR DHA OR EPA); vitamin D; magnesium. A PubMed search was conducted using the following search string: (COVID-19 OR SARS-CoV-2 OR coronavirus) AND zinc AND (PUFA OR DHA OR EPA) AND "vitamin D" AND magnesium. This search produced zero results suggesting that there have been virtually no studies examining the beneficial effects of supplementation of all four essential components together: zinc, ω-3 PUFAs, vitamin D and magnesium. Nevertheless, the four components are described or mentioned in a number of reviews of nutritional status and immune function and/or inflammation [eg, 3-6].

2. Zinc

Zinc is a vital cofactor for more than 2000 transcription factors and 300 enzymes in regulating cell differentiation and proliferation, as well as basic metabolic functions of cells [7]. Zinc deficiency is a world-wide problem with approximately 2 billion people subjected to zinc-deficient diets [7,8]. Zinc deficiency is not limited to the developing countries as it also exists in the industrialized world, mainly in the elderly [9,10]. In normal healthy adults, the plasma concentration of zinc is typically 14-23 μmol/L (0.9-1.5 μg/mL) [11].

Risk factors associated with Zn deficiency have been well reported in the literature [12-14]. Zinc deficiency can cause an imbalance in both the innate and adaptive immune systems, with severe deficiency leading to infections, skin disorders, gastrointestinal disorders, weight loss, growth retardation and male hypogonadism, amongst other symptoms [14-17]. Low zinc levels have been found to affect the function of various types of immune cells, including macrophages, neutrophils, mast cells and dendritic cells [11,18]. Zinc is also essential for the development, differentiation and activation of T cells [19]. Zinc deficiency can therefore result in impaired production, activation and maturation of natural killer cells (cell-mediated innate immunity), T cells (cell-mediated adaptive immunity) and B cells (humoral adaptive immunity) [5].

Zinc deficiency, which is commonly reported in the elderly, lowers immune function, decreases resistance to invading pathogens and increases the risk of contracting pneumonia [20,21]. Zinc deficiency also occurs frequently in patients with cardiovascular disease, chronic pulmonary disease, diabetes or obesity [22,23].

Zinc exerts its anti-inflammatory activity by inhibiting activation and signalling of NF-κB, and through controlling regulatory T cell (Treg) functions [12]. Zinc supplementation causes pro-inflammatory Th17 cells to skew towards anti-inflammatory Treg cells [24]. Zinc supplementation inhibits NF-κB through expression of the A20 protein, resulting in suppression of TNF-α, IL-1β, IL-6, IL-8, IL-12, IL-18, IFN-γ, iNOS, COX-2, GM-CSF [12,25].

Macrophages, neutrophils, and T cells are activated through elevation of cytokines including IL-1, IL-6, and TNF-α, often leading to acute respiratory distress syndrome (ARDS) [26]. IL-6, IL-8 and TNF-α levels are elevated in elderly people who are zinc deficient, as well as in the obese [17,27], and zinc supplementation has been found to reduce these levels [10].

When levels of reactive oxygen species (ROS) are elevated, as is common in zinc deficiency, oxidative damage results. Zinc supplementation decreases ROS production and this has beneficial results, especially in the aged and in diabetes mellitus [13].

A number of comprehensive reviews of zinc and its involvement in ageing, COVID-type viruses and comorbidities have been presented [eg, 27,28]. Zinc sufficiency is vital for reducing risk factors associated with COVID-19, such as obesity, diabetes, cardiovascular diseases, lung diseases and ageing [12,29]. Physiological supplementation of Zn in ageing and in age-related degenerative diseases corrects immune defects and reduces infection relapse [30].

One of the problems of zinc supplementation has been the variability of zinc bioavailability in cells. It has been found that increasing the intracellular levels of zinc using ionophores such as pyrithione can effectively decrease the replication of a variety of viruses, including the replication of SARS-CoV [31]. Unfortunately, pyrithione is not recommended for use internally, whereas it is efficacious and safe when used topically. Other proven zinc ionophores include chloroquine and hydroxychloroquine (HCQ) [12,32,33], disulfiram [33], quercetin and epigallocatechin-gallate [34], and zincophorin [35]. In addition, Rizzo [36] presented a sound rationale for ivermectin being an ionophore for zinc. A number of clinical studies are planned or underway that are based on HCQ and zinc, and ivermectin and zinc, together in some cases with an antibiotic such as azithromycin or doxycycline [37]. Interestingly, the HCQ studies are fundamentally based on testing whether zinc complements HCQ, and not whether HCQ complements zinc which would be expected if HCQ was recognized as an ionophore for zinc. A similar comment applies to ivermectin. The latest summary of ongoing studies at the time of preparing this manuscript was that of Pal et al [38].

Zinc is also known for its capacity to modulate antiviral and antibacterial immunity [12]. The antibacterial properties of zinc are well demonstrated against *S. pneumoniae* [12]. Moreover, zinc has the capacity to reduce the risk of bacterial co-infection by improving lung function through mucociliary clearance and protecting lung barrier function.

Zinc inhibits SARS-CoV RNA polymerase, and thus its replication capacity [17]. Zinc has also been postulated as a stabilizer of cell membranes which could assist in blocking virus entry to cells [39]. In this context, zinc decreases activity

of angiotensin converting enzyme 2 (ACE2) which is required for binding with SARS-CoV-2 for cell entry [12]. Wessels and co-workers [40] concluded that zinc has multiple functions in inhibiting viral entry to host cells and activity: prevention of fusion with the host membrane, inhibiting viral polymerase and ensuing replication, impairing protein translation and processing, blocking viral particle release, and destabilizing the viral envelope. It has been shown that zinc deficiency increases the leakage of the epithelium of the respiratory tract using an *ex vivo* model [41], in contrast to zinc supplementation which has been shown to improve lung integrity in a mouse model through decreased recruitment of neutrophils to the lungs [42].

According to the NIH, US National Library of Medicine, there are no formal studies evaluating zinc for COVID-19 management that have been completed and reported to date, although several trials are currently registered to test zinc as part of different regimens to treat COVID-19 [37] Nevertheless, zinc supplementation has been found to have a beneficial effect on COVID-19 patients [43,44]. A study of 47 COVID-19 patients showed that 57% of COVID-19 patients were zinc deficient. These zinc deficient patients developed more complications and had increased mortality than those with normal zinc levels [45].

Regarding the elderly, supplementation with 45 mg elemental zinc per day markedly reduced the incidence of infection in elderly subjects, ranging from 55 years to 87 years [10]. Consuming around 25-40 mg zinc per day is affordable, and less likely to induce human toxicity, as more than 200 to 400 mg per day of zinc consumption can induce adverse events [46].

3. ω-3 Polyunsaturated fatty acids (PUFAs)

ω-3 PUFAs have not received the attention they deserve in the prevention and treatment of COVID-19 and associated comorbidities. ω-3 PUFAs have properties that are significantly different from those of zinc, vitamin D and magnesium, properties that are nevertheless ideally suited to prevention and treatment of COVID-19, obesity and diabetes, cardiovascular diseases, chronic pulmonary diseases and cancer, and improving immune function and anti-inflammatory effects in general ageing [1,47-49].

SARS-CoV and SARS-CoV-2 are very similar and they are both enveloped viruses that can lead to development of ARDS. ω-3 PUFAs, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to inactivate enveloped viruses as well as to inhibit the proliferation of a range of microbial organisms [50].

The efficacy of α-linolenic acid (ALA) in treating inflammation and immune deficiency has been shown in a number of cases to be similar to that of DAH and EPA, although typically the potency is in the order DHA>EPA>ALA [eg, 49,51]. It has been reported that oil rich in ALA caused an immune modulation in cancer similar to that with fish oil, which was accompanied by a decrease in macrophage production of pro-inflammatory cytokines (eg, TNF-α and IL-6) [52].

ω-3 PUFAs have an important role in regulating macrophages as they modulate the production of cytokines and chemokines by macrophages; they change macrophage phagocytosis capacity and they convert macrophages from pro-inflammatory (M1 type macrophages) to anti-inflammatory (M2) type [53]. ω-3 PUFAs and their metabolites have a modulating effect on neutrophils as they affect neutrophil migration, phagocytic capacity and the production of ROS [53].

Weill and co-workers [51] described the action of PUFAs as having two phases in inhibiting inflammation: a promotion phase in which ω-6 PUFAs such as AA lead to the synthesis of pro-inflammatory leukotrienes and prostaglandins through the action of cyclooxygenases, lipoxygenases and cytochrome P450; and a resolution phase where ω-3 PUFAs are precursors to potent active mediators such as resolvins, maresins and protectins which inhibit the synthesis of pro-inflammatory cytokines through downregulation of the NF-κB pathway. Resolvins are sourced from EPA and DHA and protectins are sourced from DHA; they have anti-inflammatory effects by limiting leucocyte infiltration in infected tissues [51,54]. Maresins are sourced from DHA and they also resolve inflammation [51,55].

ω-3 PUFAs are notable for their influence on the properties of lipid rafts, which in turn perform an important role in the functioning of the outer leaflet of cellular membranes. ω-3 PUFAs regulate membrane properties such as membrane fluidity and signal transduction [1]. SARS-CoV has been shown to rely on lipid raft integrity for virus entry to host cells [56,57]. The entry receptor for the coronavirus, ACE2, is located in lipid rafts. The ACE2 receptor-mediated endocytosis is followed by activation of the spike protein in the viral envelope by the transmembrane serine protease 2 (TMPRSS2) which is located adjacent to the ACE2 receptor [51]. It has been shown that ω-3 PUFAs inhibit cellular entry through ACE2 and the enzymatic activity of TMPRSS2 [51,58]. The disruptive effect of ω-3 PUFAs on the integrity of lipid rafts has been described before [1], where ω-3 PUFAs were described as causing disruption to lipid rafts due to the very poor affinity of ω-3 PUFAs for cholesterol. It is therefore clear that ω-3 PUFAs have multiple inhibitory effects on viral entry into host cells.

There have been a number of clinical studies confirming the anti-inflammatory and immune response effects of ω-3 PUFA supplementation [4,5,59-61]. According to the NIH, US National Library of Medicine, there are no formal studies evaluating ω-3 PUFAs for COVID-19 management that have been completed and reported to date, although four trials are currently registered to test ω-3 PUFAs as part of different regimens [37].

4. Vitamin D

Vitamin D obtained from sunlight or dietary sources is catalysed by vitamin D-25-hydroxylase in the liver to 25-hydroxyvitamin D_3 (25(OH)D), the major circulating form of vitamin D. 25(OH)D is biologically inert until it is hydroxylated by the enzyme 1α-hydroxylase (CYP27B1) in the kidney to the active form 1α,25-dihydroxyvitamin D_3 (calcitriol, 1α,25$(OH)_2D_3$) [62].

Calcitriol has important immunoregulatory and anti-inflammatory effects that it exerts through interaction with the vitamin D receptor (VDR). The calcitriol/VDR complex can interact with different gene transcription factors that control

inflammatory responses [63]. VDR and CYP27B1 are expressed in many types of immune cells, including lymphocytes, monocytes/macrophages, dendritic cells, T and B cells [64,65], and on pulmonary epithelial cells. These immune cells can convert 25(OH)D into biologically active calcitriol [63,66]. The calcitriol/VDR complex causes transcription of the antimicrobial peptides cathelicidins and defensins. Cathelicidins disrupt bacterial cell membranes as well as enveloped viruses such as SARS-CoV-2, while defensins promote chemotaxis of inflammatory cells through increased capillary permeability [65,67].

Synthesis of vitamin D in the skin is controlled by the season, the time of the exposure during the day and the latitude [68,69]. Vitamin D is poorly synthesized above (to the north) and below (to the south) of 35° latitude during winter months [70]. Lockdowns, implemented to minimize the spread of COVID-19, are therefore detrimental to vitamin D synthesis as people are prevented from going out from their homes and absorbing the sunshine, which has a cumulative effect in the winter months when COVID-19 is more prevalent. The Black and Asian populations produce less vitamin D as a result of a higher skin melanin content than those with white skin [71]. Excess exposure to sunlight is the major cause of skin cancer [72]. However, there is an increased incidence of skin cancer and other cancers in countries with low levels of sunlight compared with those countries with higher levels of sunlight throughout the year [73,74], supporting the proposition that sunlight is beneficial for synthesis of vitamin D and subsequent prevention of cancers. There have been a number of reports where low sun exposure has been shown to have a negative impact on a range of health issues [75-77]. The advantage of sun exposure in providing vitamin D needs to be sensibly balanced against the potential risk of skin cancer from excessive sun exposure [78].

In the early stages of acute inflammation, vitamin D inhibits the proliferation of Th1 and Th17 cells and their abnormal release of IFN-γ, TNF-α, IL-1, IL-2, IL12, IL-23 and IL-17, IL-21 [65]. During the resolution phase of inflammation, vitamin D-mediates differentiation of Th2 cells and release of their anti-inflammatory cytokines (IL-4 and IL-10), evading the organ damage that could be caused by an excessive immune response [65]. Vitamin D has powerful anti-inflammatory properties that play an important role in controlling immune function in pulmonary infection; eg, it inhibits the effects of TNF-α, it inhibits NF-κB activity in immune cells, it inhibits the activation of inflammasomes and hence release of IL-1β, and it decreases expression of IL-6, a major contributor to the so-called 'cytokine storm' [65,79].

The immune response acts in concert with the inflammatory response. The innate immune system acts as the first line of defence against invading pathogens such as viruses. Calcitriol enhances that defence by recruiting neutrophils, monocytes/macrophages and dendritic cells which kill and clear the viral pathogens, ultimately initiating the adaptive immune response. This response can be overactive resulting in the cytokine storm. Calcitriol inhibits this chronic immune response by downregulating the toll-like receptors (TLRs) that identify the viral pathogens initially, and inhibits the TNF-α/NF-κB and IFN-γ signalling pathways. Calcitriol shifts the T cell profile from the pro-inflammatory Th1 and Th17 forms to the anti-inflammatory Th2 and Treg forms, respectively [80]. Tregs provide a major defence against inflammation, releasing anti-inflammatory cytokines IL-10 and TGF-β. Treg levels are markedly decreased in

severe COVID-19 disease, in contrast to high levels of Treg correlating with reduced levels of viral disease [81].

Natural killer cells are innate immune cells and they are known to possess strong antiviral activity as well as anticancer activity [82]. The count and activity of natural killer cells have been shown to be reduced below normal in COVID-19 patients, and vitamin D has been found to increase the activity of natural killer cells [82].

Although there is inconsistency in the data, it is apparent that vitamin D deficiency is influential in increasing risk of acute respiratory tract infections [83], particularly when considering the decrease in natural synthesis of vitamin D in winter-time when acute respiratory infections are most prevalent. Ali [84] conducted a study of COVID-19 cases and mortality in 20 European countries, finding that vitamin D status correlated negatively with COVID-19 cases but not with mortality. The effectiveness of vitamin D sufficiency in reducing risk of acute viral respiratory tract infections and pneumonia was also shown. Similar results were reported by Kara and co-workers [85], who also discussed the link between latitude, temperature and humidity and season on viral respiratory tract infections.

Allegra and co-workers [86] reported on the deficiency and supplementation of a range of vitamins including vitamin D, in particular in correlating hypovitaminosis with risk of contracting COVID-19 and associated mortality. They reported that there were positive and indeterminate results in their analysis of multiple studies. Vitamin D levels were particularly reduced in the ageing populations of Italy, Spain, and Switzerland, which were the most susceptible populations in relation to SARS-CoV-2 infection [87]. Additionally, Annweiler and co-workers [88] analysed a range of reports with the conclusion that inverse correlations were found between 25(OH)D levels in patients and COVID-19 incidence and mortality. Other reports have also covered the influence of vitamin D on outcomes of COVID-19 patients with the typical finding that vitamin D supplementation leads to an improved outcome for these patients and that vitamin D deficiency increases the risk and susceptibility for severe COVID-19 disease and mortality [69,84,87,89-99].

In another review, Lau and co-workers [100] found that vitamin D deficiency was highly prevalent in patients with severe COVID-19, which correlated in turn with obesity, male sex, advanced age, population concentration in northern climates, coagulopathy and immune dysfunction. A further meta-analysis found that vitamin D deficiency increased risk of severe infections and mortality of the critically ill [101]. Deficiency of vitamin D has been further claimed to increase the risk of contracting osteoporosis, cancer, diabetes, multiple sclerosis, hypertension, and inflammatory and immunological diseases [102]. Although vitamin D and the benefits of supplementation in preventing cancer have been discussed previously [1], it is of note that a number of researchers have demonstrated that the risk of cancer incidence and fatality is reduced with vitamin D supplementation [eg, 103-105]. The mechanism of action of vitamin D in reducing cancer risk has also been addressed in a number of reviews [eg, 106-108].

It has been specified that a reasonable level of 25(OH)D in serum is at least 30 ng/mL (75 nmol/L) [93,109], with a preference for 40–60 ng/mL (100–150 nmol/L) to ensure good health, particularly in the elderly [69,110].

In summary, vitamin D impedes the entry and replication of SARS-CoV-2, reduces the levels of pro-inflammatory cytokines, increases the levels of anti-inflammatory cytokines and increases the production of natural antimicrobial peptides [111].

5. Magnesium

Magnesium is an essential element in the optimal biological functioning of the human body. Magnesium is the second most abundant intracellular cation in the human body and it is fundamental for oxidative phosphorylation, glycolysis, DNA transcription, and protein synthesis [112]. Magnesium levels are not routinely analysed in clinical practice [113] which means there has been limited reporting of magnesium correlations for COVID-19 patients [113,114]. Despite this, there have been some reports of magnesium status being lower in severe COVID-19 cases than in less severe cases [115-117]. On the other hand, there have been a number of excellent reviews of magnesium and its essentiality in maintenance of proper immune function and control of oxidative stress and low-grade inflammation, particularly in the elderly [eg, 112,118-122].

Magnesium is essential for the activation of vitamin D [122,123]. Magnesium and vitamin D are therefore both important for immune function and cellular stability and sufficiency of both is required to counteract the detrimental effects of COVID-19 development [122].

Deficiency of magnesium is common and it has been estimated that in a given population up to 30% may have a magnesium deficiency [122]. Magnesium is principally stored in bone (>50%) with only ~1% in serum [124]. Magnesium homeostasis is maintained by absorption from the gastrointestinal tract, renal excretion and exchange from bone. Estimates of magnesium sufficiency are therefore dubious if reliant on serum analysis alone [118]. However, 0.75 mmol/L has been suggested as the serum level below which magnesium deficiency exists [125], and 0.85 mmol/L as the required level for magnesium sufficiency [118].

Magnesium has anti-inflammatory and anti-oxidative effects, as well as providing vasodilation and neuroprotection [120]. Magnesium suppresses NF-κB, expression of IL-6 and TNF-α, and levels of C-reactive protein (CRP) [6,121,126]. Magnesium therefore regulates the cardiovascular, digestive, neurological and respiratory systems, contributing significantly to maintenance of normal human health [120]. In this context, magnesium dietary intakes correlate negatively with cardiovascular disease, kidney disease and diabetes [118,127].

6. COVID-19

SARS-CoV-2 is an insidious virus that causes the disease COVID-19. There are many similarities between SARS-CoV-2 and the earlier coronavirus SARS-CoV. In

order to present the overall essentiality of ensuring sufficiency of zinc, ω-3 PUFAs, vitamin D and magnesium, the key contributing stages of SARS-CoV-2 incursion and COVID-19 development will be discussed. These are viral entry, the involvement of the immune system and inflammation, and the subsequent cytokine storm that causes the eventual morbidity and mortality that is associated with COVID-19.

6.1 Viral entry

SARS-CoV-2 enters the host cells via the angiotensin-converting enzyme 2 (ACE2) receptor, in the same manner as SARS-CoV [128]. The spike protein of SARS-CoV-2 binds to ACE2, enabling endocytosis, which is followed by activation of the S protein in the viral envelope utilizing the transmembrane serine protease 2 (TMPRSS2), a membrane-bound enzyme located adjacent to the ACE2 receptor [51]. At the same time, the ADAM17 (disintegrin and metalloproteinase domain 17) 'sheddase' is activated by the SARS-CoV-2-ACE2 complex which in turn leads to ACE2 ectodomain shedding. Activation of the ADAM17 sheddase may also cause cleavage of TNF-α and IL-6 as well as other pro-inflammatory mediators [128]. It should be noted that the ACE2-binding affinity of the of S protein of SARS-CoV-2 is 10- to 20-fold higher than that of SARS-CoV [129], suggesting that SARS-CoV-2 is significantly more infectious than its predecessor SARS-CoV.

The balance of the renin-angiotensin system (RAS) is vital in controlling host-cell entry of viruses as well as associated comorbidities, as RAS regulates blood pressure. RAS is essentially a balance between ACE and ACE2, as illustrated in Figure 1. The ACE pathway requires conversion of angiotensin (Ang) I to Ang II and subsequent binding to the AT1 receptor (AT1R), which has dire consequences such as vasoconstriction, proliferation, inflammation, and apoptosis [91]. The alternative route involves conversion of Ang I and Ang II to angiotensin 1-9 and angiotensin 1-7, respectively, through the enzymatic action of ACE2. Angiotensin 1-9 is also converted to angiotensin 1-7 by ACE.

ACE2 is required for viral entry to host cells, but it is also desirable for conversion of Ang I and Ang II to angiotensins 1-9 and 1-7, respectively, leading to activation of the Mas receptor. Figure 1 shows that this in turn will cause positive pathology in terms of vasodilation, and anti-inflammatory, anti-oxidative and anti-fibrosis effects [130].

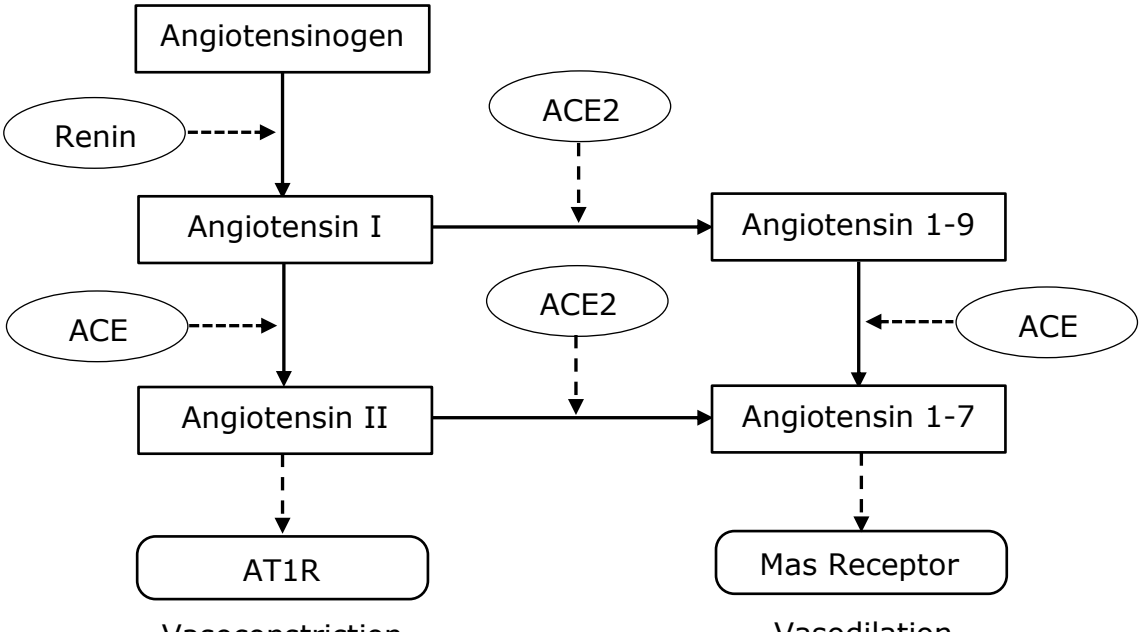

Figure 1. RAS pathways showing the balance between ACE and ACE2.

There has been fairly extensive discussion about the contradictory actions of ACE2 in viral entry to host cells and its regulation of the RAS where modulation of RAS has a positive pathological effect. The ACE2 receptor is expressed in lung tissues, and a range of other tissues such as nose, heart, endothelium, kidney and intestine [131,132]. It has now been resolved that once the virus binds to ACE2, it effectively removes it from further action, promoting ACE activity which in turn leads to production of more Ang II. The removal of ACE2 from action therefore causes the virus to have a free run allowing it to proliferate, leading to enhanced morbidity.

The expression of ACE2 has been found to be lower in males than in females and lower in older adults than in young people, which could explain the higher incidence of deaths in elderly males with COVID-19 [130,133]. This category of patients has a worse prognosis when they are also implicated with comorbidities such as cardiovascular diseases, diabetes, hypertension, and obesity, all of which are stimulated by RAS [130]. It is therefore important to enhance the expression of ACE2 and its activity, and at the same time ensure that the entry of the virus to host cells is inhibited. This can be achieved by ensuring that sufficient levels of zinc, ω-3 PUFAs, vitamin D and magnesium are maintained at all times during prevention and treatment of COVID-19.

It should be noted that although there are no reported studies of the effect of zinc on ACE2 for host-cell entry, zinc does protect the human body from virus entry by improved mucociliary clearance of viruses as well as preserving tissue barriers [42]. It has been recognized that enhanced expression of ACE2 by calcitriol alleviates acute lung injury induced by SARS-CoV-2 [134-136]. Calcitriol also supresses renin activity and therefore reduces the generation of angiotensin II which causes pulmonary vasoconstriction [134]. As stated above, binding of ACE2 and cellular entry are inhibited by ω-3 PUFAs [51,58].

6.2 The immune system

The immune system provides two lines of defence: innate and adaptive immunity. Innate immunity is the first line of defence, reliant on mucosal barriers, monocytes, macrophages, neutrophils, eosinophils, and dendritic cells. Adaptive immunity is the process by which immunological memory to a specific

antigen is created but more slowly than innate immunity. Dendritic cells also function as antigen-presenting cells, activating B and T lymphocytes of the adaptive immune response [53].

Mast cells are present in the submucosa of the nasal cavity and respiratory tract where they provide a protective barrier against microorganisms and they can be virus-activated [29]. When activated, mast cells initially release preformed inflammatory molecules such as histamine and proteases, while late activation activates the synthesis and release of pro-inflammatory IL-1 family members, including IL-1, IL-6, and IL-33 [137]. Mast cells therefore normally release a wide range of pro-inflammatory mediators. Vitamin D diverts the release characteristics of mast cells to produce and excrete IL-10 without inducing degranulation of pro-inflammatory mediators [138]. IL-10 is an important anti-inflammatory cytokine that inhibits the production of pro-inflammatory cytokines, such as IFN-γ, IL-2, IL-3, TNF-α, and GM-CSF [139].

Macrophages are fundamental to the innate immune system as they scavenge invading pathogens: they recognize invading pathogens through use of pathogen-associated molecular patterns which are in turn recognized by TLRs present on their surface. Macrophages then phagocytose the invading pathogen and at the same time secrete ROS and a large range of cytokines and chemokines to recruit and activate other types of immune cells from both the innate and the adaptive immune systems [53]. The most damaging cytokines released by macrophages when over-activated are IL-1β, IL-6 and TNF-α [140].

Eosinophils release pro-inflammatory mediators, including degranulated cationic proteins, synthesized eicosanoids, and cytokines [141]. Neutrophils are recruited to the initial site of inflammation where they also have a role in removing pathogens. Neutrophils can also interact with the adaptive immune system by promoting naïve T cells to transition into T helper 1 (Th1) cells [53].

T cells are thymus-derived lymphocytes. T cells can be classified into helper (Th) cells that regulate the function of other immune cells, and cytotoxic T cells that destroy virus-infected cells. Th cells differentiate into Th1, Th2, Th17 and Th22 cells. Th1 cells secrete IFN-γ; Th2 cells secrete IL-4; Th17 cells secrete IL-17A, IL17-F, IL-21, and IL-22; and Th22 cells secrete IL-22. Th1 and Th17 cells are pro-inflammatory, whereas Th2 cells are essentially anti-inflammatory [53]. Regulatory T cells (Tregs) suppress the activation of other immune cells such as Th1 cells, Th17 cells, B cells, macrophages or dendritic cells, through secretion of IL-10 and TGF-β [53].

The impact provided by the various contributing immune system cells on the SARS-CoV and SARS-CoV-2 viruses is given in Table 1. It can be seen that the release of cytokines and chemokines is potentially huge, leading to the potential for production of the cytokine storm.

Table 1. Mediators released/activated in cells in SARS and COVID-19

Cell Type	**Mediators released/activated**	**References**
Mast cells	Histamine, tryptase, NF-κB, IL-1α/β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18, IL-25, IL-33, TNF-α, IFN-γ, TGF-β, CCL2, CCL3, GM-CSF, VEGF,	29,142-146

	PDGF, SCF, PGE2, ROS, TLR2, c-Kit	
Monocytes/macrophages	NF-κB, TNFα, IL-1α/β, IL-1RA, IL-6, IL-8, IL-10, IL-12, IFN-γ, TGF-β, ROS, TLR2, TLR4	6,110,147-150
Eosinophils	IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-11, IL-12, IL-13, IL-16, IL-18, IL-25, TNF-α, IFN-γ, TGF-α/β, VEGF, GM-CSF	145,151-154
Neutrophils	IL-1α/β, IL-1RA, IL-3, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-16, IL-17, IL-18, IL-23, Th1/Th2, TGF-α/β, IFN-α, IFN-γ, TNF-α, G-CSG, GM-CSF, SCF, FGF, VEGF, CCL2, ROS, TLR2, TLR4	155-158
Dendritic cells	IL-6, IL-10, IL-12, TNF-α, CCL3, RANTES, IP-10, CCL2	110,142,159
Th1	IFN-γ, IL-1β, IL-2, IL-12, TNF-α	110,148
Th2	TGF-β, IL-4, IL-5, IL-9, IL-10, IL-13	110,148
Th17	IL-17A, IL-17F, IL-21, IL-22	110,160
Treg	IL-10, TGF-β	53,110

Table 2 shows the key immune cells and regulators that contribute to immune function and inflammation together with the correcting effects of zinc, ω-3 PUFAs, vitamin D and magnesium on each of these immune cells and regulators when immune function and inflammation are over-activated.

Table 2. Inhibition(↓)/activation(↑) of immune cells cells/regulators

Cell/regulator	Zinc	ω-3 PUFAs	Vitamin D	Magnesium
Mast cells	↓ [161,162]	↓ [144,163,164]	↓ [138,165-167]	↓ [168,169]
Monocytes	↓ [170,171]	↓ [172,173]	↓ [147]	↓ [174,175]
Macrophages	↓ [176]	↓ [177,178]	↓ [179,180]	↓ [175,181,182]
Neutrophils	↓ [171,183,184]	↓ [185,186]	↓ [187,188]	↓ [181,189]
Dendritic Cells	↓ [190,191]	↓ [192,193]	↓ [63,194,195]	↓ [196]
Eosinophils	↓ [171,197,198]	↓ [172,185,199]	↓ [200,201]	↓ [202]
Th1/Th2 ratio	↓ [203,204]	↓ [205,206]	↓ [207]	↓ [208]
Th17	↓ [24,209-211]	↓ [212-214]	↓ [215,216]	—
Treg	↑ [24,211,217,218]	↑ [213,219-221]	↑ [222-224]	—
Inflammasome/ caspase-1	↓ [225,226]	↓ [227-229]	↓ [79,230-232]	↓ [233,234]
NF-κB	↓ [12,17,25,235]	↓ [132,236,237]	↓ [79,238-240]	↓ [121,174,241]

— indicates no literature reference found

6.3 Cytokine storm

The uncontrolled release of immune cells and excessive release of pro-inflammatory cytokines has been termed the 'cytokine storm'. The cytokine storm normally presents as systemic inflammation, excessive oxidative stress and multiple organ failure [29,51], predominantly resulting in ARDS. The key to counteracting the cytokine storm lies in counteracting excessive inflammation. This can be largely addressed through maintenance of sufficiency of the essential nutrients zinc, ω-3 PUFAs, vitamin D and magnesium. Table 3 gives the key pro-inflammatory cytokines and other mediators involved in a cytokine storm, together with the inhibitory effects of zinc, ω-3 PUFAs, vitamin D and magnesium. It can be seen that these four nutrients are widely effective in inhibiting the key pro-inflammatory mediators of the cytokine storm.

Table 3. Key pro-inflammatory mediators in a cytokine storm.
↓ inhibits the mediator.

Mechanisms	**Effect of Zinc on mediator [Refs]**	**Effect of ω-3 PUFAs on mediator [Refs]**	**Effect of Vitamin D on mediator [Refs]**	**Effect of Magnesium on mediator [Refs]**
TNF-α	↓ [9,235]	↓ [177,242-244]	↓ [245-248]	↓ [126,174,249]
IFN-γ	↓ [217,218,250]	↓ [193,212,244]	↓ [247,248,251-253]	↓ [208,249]
IL-1β	↓ [9,210,254]	↓ [177,227,244,255, 256]	↓ [79,231,232,248, 257]	↓ [182,233,249,258, 259]
IL-6	↓ [17,260]	↓ [177,212,243,244, 256]	↓ [65,248,261,262]	↓ [121,126,174,182, 263]
IL-12	↓ [264]	↓ [172,265]	↓ [111,195,266,267]	—
IL-17	↓ [209,210,268]	↓ [185,193,212,244]	↓ [216,248,269,270]	—
IL-18	↓ [271]	↓ [228]	↓ [272]	—
IL-33	↓ [273]	↓ [274]	↓ [275]	—
CCL2 (MCP-1)	↓ [9,171]	↓ [276-279]	↓ [280-282]	↓ [263,283]
CCL3 (MIP-1α)	↓ [284]	↓ [276,285]	↓ [216,286]	—
C-reactive protein (CRP)	↓ [287-289]	↓ [290-292]	↓ [93,293,294]	↓ [121,126,295]
GM-CSF	↓ [296]	↓ [297,298]	↓ [299-302]	—
NF-κB	↓ [12,25,226,235]	↓ [132,236,237]	↓ [79,238-240]	↓ [121,174,241]

— indicates no literature reference found

7. Ageing, obesity and non-communicable diseases

Deficiencies in zinc, ω-3 PUFAs, vitamin D and magnesium have been shown above to provide significant risk factors for severe COVID-19 disease as well as for pre-existing conditions such as ageing, obesity/diabetes, cardiovascular diseases, chronic respiratory diseases and cancer. All of these comorbidities are accompanied by systemic inflammation which likely impacts on the COVID-19 outcome [29].

Table 4 lists the immune cells and mediators that are released in COVID-19, the cytokine storm, ageing, obesity/diabetes and the principal non-communicable diseases. It can be seen that many of the mediators, particularly those that are key pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α and IFN-γ, are common to COVID-19, the cytokine storm (which in turn is part of COVID-19) and the listed comorbidities. The entry in Table 4 for chronic respiratory diseases has been taken to be the same as the cytokine storm, which is the principal force behind creation of ARDS.

Table 4 Key cells and mediators associated with COVID-19, cytokine storm, ageing and comorbidities

Comorbidity/Activity	Cells/Mediators/Transcription factors	References
COVID-19	Mast cells, neutrophils, eosinophils, monocytes, macrophages, dendritic cells, NF-κB, IL-1β, IL-1RA, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-17, IL-18, IL-21, IL-22, IL-33, TNF-α, IFN-γ, GM-CSF, G-CSF, CCL2, CCL3, IP-10, Th1/Th2, PDGF, VEGF, FGF, CRP	29,133,142,148,160,303
Cytokine storm	IL-1β, IL-6, IL-7, IL-8, IL-9, IL-12, IL-17, IL-18, IL-33, TNF-α, IFN-γ, CCL2, CCL3, FGF, G-CSF, GM-CSF, IP-10, PDGF, VEGF, CRP	29,142,155,160,304
Ageing	IL-1, IL-1RN, IL-2, IL-6, IL-8, IL-12, IL-13, IL-18, CRP, IFN-γ, TGF-β, TNF-α, SAA	305,306
Obesity/diabetes	M2→M1, Th2→Th1, Treg→Th17, B cells, IL-1β, IL-6, IL-7, IL-22, IFN-γ, TNF-β, CCL2, TNF-α	305,301
Cardiovascular diseases	NF-κB, IL-1β, IL-2, IL-4, IL-6, IL-17, GM-CSF, MMP-2, MMP-9, CCL2, ERK1/2, P38 MAPK, TNF-α, IFN-γ, HIF-1α, TLR2, TLR4	302,309
Chronic respiratory diseases	IL-1β, IL-6, IL-7, IL-8, IL-9, IL-12, IL-17, IL-18, IL-33, TNF-α, IFN-γ, CCL2, CCL3, FGF, G-CSF, GM-CSF, IP-10, PDGF, VEGF	29,142,155,160,304
Cancer	NF-κB, p53, COX-2/PGE2, TNFα, IL-1β, IL-6, IL-8, p27, PPARα,γ, GSK-3, EGFR, HER2, VEGF, Cyclin D1, c-Myc, PTEN, MDM2, HIPK2, A20, p21, TGF-β, PARP, caspases-3,7,8,9, Bcl-2, Bcl-xL, Bax, cytochrome c, ROS, iNOS, MMP9, HIF-1α, TLR4,	1

7.1 Ageing

As the human body ages, there is a gradual decline in functioning of the innate and adaptive immune systems, designated immunosenescence, as well as an increase in the levels of pro-inflammatory cytokines IL-1β, IL-2, IL-6, IL-8, TNF-α and IFN-γ, as well as CRP [148,305,310]. There is also a decline in ACE2 expression, similarly to COVID-19 [148]. Ageing also produces excess ROS production which can initiate pro-inflammatory generation through activation of transcription factors such as NF-κB [148]. T-cell function has been found to become increasingly defective in the elderly, decreasing immune function [20].

Maintenance of healthy functioning of cells is of increasing importance as ageing progresses. Working against this, deficiencies in one or more of zinc, ω-3 PUFAs, vitamin D and magnesium will lead inevitably to a diminution in immune function and an increase in levels of inflammatory mediators [21,27,311]. Deficiencies of zinc, ω-3 PUFAs, vitamin D and magnesium increase with ageing, frequently contributing to age-related diseases such as diabetes, cardiovascular diseases and chronic pulmonary diseases [27].

Diet is very important for adequate intake of zinc, ω-3 PUFAs and magnesium as the importance and interest in quality of food diminishes with old-age, as well as

the degree of absorption [312] In addition, the exposure of the aged to sunlight becomes severely limited, leading to diminished vitamin D levels.

7.2 Obesity/diabetes

Obesity is related to the accumulation of pro-inflammatory cells in visceral adipose tissue, which can lead to insulin resistance and to diabetes mellitus [151]. Obesity is associated with low-grade inflammation, which in turn is associated with diminution of the innate and adaptive immune responses. Low-grade inflammation is linked to adipocyte hypoxia and dysfunction [307]. There is a significant release of pro-inflammatory cytokines (eg, IL-1β, IL-6, TNF-α) that activate in turn macrophages, T cells and B cells, creating an auto-regenerating loop [307,313]. Obesity is also associated with increased oxidative stress [314].

Zinc deficiency has been shown in a number of studies to be associated with obesity and diabetes [315-317]. Zinc is essential for the normal physiological processing of insulin and is therefore directly associated with diabetes [318].

The ω-6/ω-3 PUFA ratio has increase dramatically over the past 50 years and it has contributed to the increased proportion of the population who are obese [319]. It has been shown that this trend can be reversed by increasing the EPA and DHA intakes [319]. It has been recommended that fish oil emulsion supplement be administered to those who are obese and at risk of contracting COVID-19, due to the immune modulatory properties of EPA and DHA [320].

Obesity increases the risk of vitamin D deficiency, mainly due to the higher adiposity of the obese individual. Vitamin D is fat-soluble and is predominantly stored in the adipose tissues, leading to low levels of vitamin D in the circulation [321]. Low vitamin D levels have been reported consistently across age groups, ethnicity and geography [322,323]. Meta-analyses found that vitamin D deficiency correlated with increased obesity [321,324]. Vitamin D supplementation has been shown to reduce insulin resistance [325] and diabetes mellitus has been found to correlate with vitamin D deficiency in older adults [326].

There is a positive relationship between magnesium deficiency and obesity and chronic inflammation [327]. In turn, obesity is a major risk factor for chronic diseases which depend on chronic inflammation, such as diabetes, cardiovascular diseases and cancer [327].

7.3 Cardiovascular diseases

A large proportion of COVID-19 patients have risk factors associated with cardiovascular diseases [328]. The high levels of inflammation associated with COVID-19 can induce cardiovascular diseases [80,328]. Studies of COVID-19 individuals with underlying cardiovascular disease were at increased risk of severe disease and mortality [329].

Choi and co-workers [330] reviewed the literature covering zinc status and cardiovascular diseases. They found that zinc deficiency was associated with atherosclerosis, hypertension, myocardial infarction, atrial fibrillation and

congestive heart failure. Similarly, Jurowski and co-workers [331] had reviewed the literature, reporting that zinc deficiency correlated with hypertension, atherosclerosis and heart failure. Further reports support the fact that zinc deficiency is associated with cardiovascular diseases [22,23].

The cardioprotective effects of n-3 PUFAs and their metabolites are ascribed mainly to their immunomodulatory properties. Emerging evidence demonstrates the ability of ω-3 PUFAs to reduce circulating levels of inflammatory chemokines, cytokines, and the pro-inflammatory metabolites derived from ω-6 PUFAs [332,333]. A number of studies have found that higher consumption of ω-3 PUFAs lowers the number of deaths related to cardiovascular disease [334-337]. Darwesh and co-workers [338] presented a detailed report on the positive effects of ω-3 PUFAs in cardiovascular diseases, which included stabilization of atherosclerotic plaques, reducing the incidence of thrombus formation, enriching cellular membranes and altering the structure of lipid rafts and their function to benefit the treatment of cardiovascular diseases.

There is a strong correlation between obesity and vitamin D deficiency, as well as between obesity and cardiovascular disease. It would therefore be anticipated that there would be a benefit in supplemental vitamin D for obese patients at risk of cardiovascular disease [339]. A study of 137 elderly Brazilian patients found that 65% were vitamin D deficient and there was a strong association between vitamin D deficiency and the risk of heart failure [340].] A number of literature reviews have examined the association between vitamin D deficiency and the incidence of cardiovascular diseases, with the conclusion that vitamin D decreases inflammation and pro-inflammatory cytokines causing a strong association with cardiovascular diseases [308,341,342].

The anti-inflammatory and anti-oxidative effects of magnesium provide cardiovascular protection [119,120]. Qu and co-workers [127] provided a meta-analysis that showed an inverse correlation between magnesium serum concentrations and the risk of total cardiovascular events.

7.4 Lung diseases

Lung diseases include pneumonia, bronchitis and asthma. The most common lung disease associated with COVID-19 is acute respiratory distress syndrome (ARDS), promoted most often by the cytokine storm, and which is often lethal [51]. ARDS occurs in approximately 10% of COVID-19 patients [51].

Meydani and co-workers [20] found that nursing home elderly who were zinc deficient were more likely to contract pneumonia with its subsequent consequences. Further reports support the fact that zinc deficiency is associated with chronic pulmonary diseases [21,23]. Skalny and co-workers [12] deduced that zinc has the propensity to alleviate COVID-19 through its properties of reducing inflammation, improving mucociliary clearance and promoting antiviral and antibacterial immunity.

Weill and co-workers [51] discussed the properties of ω-3 PUFAs, which include interference of viral entry and replication and inhibition of inflammation, leading to improvement of the outcome of critically ill patients with ARDS. It was shown in a study where bronchoalveolar lavage fluid was added to A549 cells that by

increasing the ratio of ω-3:ω-6 PUFAs, there was a decrease in levels of NF-κB, COX-2 and PGE2, and an increase in release of IL-10 and PPARγ [343].

It has been noted that there is a strong link between seasonality of low vitamin D levels and occurrence and prevalence of influenza in winter [80]. It has also been reported that a high percentage (>80%) of chronic obstructive pulmonary disease patients had low vitamin D levels [344]. The association between higher vitamin D levels and improved lung function has also been reported [345-347]. Moreover, it has been reported that vitamin D deficiency is associated with occurrence of respiratory disease and ensuing mortality [90,347-349].

The role of magnesium in lung function was discussed by de Baaij and co-workers [124], where magnesium was described as having three roles: a strong vasodilator and bronchodilator effect, regulation of the release of acetylcholine and histamine, and as an anti-inflammatory agent. Magnesium was therefore suggested as a useful treatment for asthma and chronic obstructive pulmonary disorder. Micke and co-workers [114] also discussed magnesium and lung function in some detail, with a similar analysis of the anticholinergic, antihistaminic and anti-inflammatory effects of magnesium.

7.5 Cancer

Cancer has been discussed in the context of essentiality of sufficiency of zinc, ω-3 PUFAs and vitamin D [1]. The opportunity of including magnesium as a further essential component in prevention and treatment of cancers is taken here, as magnesium is essential for the activation of vitamin D [122,123]. Magnesium, as discussed above, is also active in regulating the immune system and controlling untoward oxidative stress and inflammation [119,120] which are prevalent in the early development of cancers [350].

8. Discussion

COVID-19 and its virus SARS-CoV-2 have provided an ideal opportunity to reset the approach to prevention and treatment of non-communicable diseases, particularly those that occur predominantly in the aged. COVID-19 has been shown to be linked to comorbidities such as senescence occurring in the aged, obesity/diabetes which are more severe in the aged, and cardiovascular diseases and chronic pulmonary diseases which are more prevalent in the aged, as well as cancers. It is therefore opportune to examine carefully the prevention and treatment of COVID-19 and those diseases, with particular attention to those features and characteristics that are common to these diseases. The most outstanding common features are inflammation and overactivity of the innate and adaptive immune systems. Control of inflammation and the immune system are fundamentally dependent on sufficiency of the essential nutrients zinc, ω-3 PUFAs, vitamin D and magnesium.

This paper has been directed towards an appreciation of the benefits of having sufficiency of zinc, ω-3 PUFAs, vitamin D and magnesium. These four components are essential as they are natural to the normal functioning of cells and multiple other components of the human body. They are extremely safe when supplemented in a controlled manner. Control in the aged (eg, 65 years and older) can be maintained by annual analyses of their serum levels. This can

be achieved with government support, as well as by government supplies of supplements where necessary. The cost of this service to those over 65 would be small compared with the potential savings in hospitalization and critical care costs. As an example, a German estimate of the effect of supplementing vitamin D alone on the cost savings of cancer alone in Germany showed a cost saving of approximately €254 million per year with a prevention of almost 30,000 deaths to cancer per year [351].

Zinc, ω-3 PUFAs, vitamin D and magnesium are pleiotropic as they allow, and in fact boost, the functioning of granulocytes such as mast cells, neutrophils and eosinophils, as well as monocytes/macrophages, dendritic cells, T cells and B cells in normal conditions and when there are minor invasions of pathogens such as minor viral and bacterial infections. In contrast, zinc, ω-3 PUFAs, vitamin D and magnesium all act to suppress hyperinflammation and major disruptions of the immune system that occur when there is a significant invasion by viral or bacterial pathogens such as SARS-CoV-2 or non-communicable diseases such as diabetes, cardiovascular disease or chronic pulmonary disease. In these situations, zinc, ω-3 PUFAs, vitamin D and magnesium have the ability to suppress excessive inflammation and dysregulation of the immune system. These nutrients are therefore essential in all aspects; when present in sufficiency they are directed towards ensuring good health for humans at all times and for all ages. This is not normally the case with non-natural drugs that are prescribed for treatment of particular pathological conditions.

Vaccines are rarely 100% in their prevention of transmission and their prevention of humans contracting the particular disease; there are potential problems with mutations and diminution of their effectiveness. It is of note that vaccines perform their function through the adaptive immune system, whilst zinc, ω-3 PUFAs, vitamin D and magnesium affect both the innate and adaptive immune systems. Supplementation of the four nutrients in treatment of COVID-19 is therefore desirable, especially if this supplementation is beneficial in preventing or treating non-communicable diseases or reducing the adverse effects of ageing.

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Declaration of competing interest

There is no conflict of interest.

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Highlights

Title: Essential sufficiency of zinc, ω-3 polyunsaturated fatty acids, vitamin D and magnesium for prevention and treatment of COVID-19, diabetes, cardiovascular diseases, lung diseases and cancer

- Zinc, ω-3 PUFAs, vitamin D and magnesium are inexpensive, safe and essential, especially for the aged
- These nutrients inhibit viral entry, viral proliferation, inflammation and immune dysfunction
- These nutrients will assist in preventing and alleviating COVID-19 and associated comorbidities
- Levels of these nutrients should be checked annually and supplemented for sufficiency in the aged
- Costs of checking and provision of supplements should be at government expense for the aged