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VIEWPOINT

Nutrition and the Covid-19 pandemic: Three factors with high impact on community health

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Abstract *Aims:* In the course of the COVID-19 pandemic, multiple suggestions have been delivered through websites and social media referring to natural substances and various kinds of supplements with thaumaturgical properties in preventing and/or fighting the coronavirus infection. Indeed, there is no clinical trial evidence that a dietary or pharmacological supplementation of any particular substance will increase the effectiveness of the immune defences. There are however three nutritional issues that deserve special attention under the present circumstances, namely vitamin D deficiency, excess salt intake and inappropriate alcohol consumption. Here is a short review of the current knowledge about the possible role of these factors in the immunity defence system and their potential impact on the modulation of the immune response to SARS-COV2 infection.
Data synthesis: For all of these factors there is convincing evidence of an impact on the immune defence structure and function. In the absence of RCT demonstration that increased ingestion of any given substance may confer protection against the new enemy, special attention to correction of these three nutritional criticisms is certainly warranted at the time of COVID pandemic.
Conclusions: We propose that the inappropriate intake of salt and alcohol and the risk of inadequate vitamin D status should be object of screening, in particular in subjects at high mortality risk from SARS-COV 2 infection, such as institutionalised elderly subjects and all those affected by predisposing conditions.

Introduction

In the course of the COVID-19 pandemic, multiple suggestions have been delivered through websites and social media referring to natural substances and various kinds of supplements which were attributed thaumaturgical properties in preventing and/or fighting the coronavirus infection. For some of these substances such as several minerals and vitamins, it is true that they are functional to the efficiency of the immune system: it does not follow however that a dietary or pharmacological supplementation of these substances above the quantities recommended in the context of a correct diet, will increase the effectiveness of the immune defences. In fact, during the pandemic, the World Health Organization provided very simple indications regarding the cornerstones of a correct and adequate diet, which recall the general Guidelines for healthy nutrition. They reflect a Mediterranean-like dietary model, based on the prevalent consumption

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of fresh and unprocessed plant foods and on the avoidance of excessive consumption of salt, sugars and saturated fats [1].

Review articles have also been published in scientific journals that specifically discuss the role of nutrition in protecting against infectious diseases. An authoritative example of such reviews proposed to double the recommended intake of some vitamins and minerals which have a recognized role in the correct functioning of the immune system, through the supplementation of a multimineral and vitamin preparation [2]. In particular, the article highlighted the possible role of zinc, vitamin C and omega 3 fatty acids in relation to the severity of the inflammatory process aroused by the viral agent. Although the suggestions provided are inspired to caution and moderation, it should be noted that there is no RCT evidence of the concrete benefits attributed to the aforementioned measures. Therefore, the authors' advice must be taken as authoritative expert rather than evidence based recommendation.

There are however three nutritional issues that, in our view, deserve special attention under the present circumstances: 1) vitamin D deficiency, 2) excess salt intake and 3) inappropriate alcohol consumption. All of these three factors have been object of extensive investigation with regard to their effects on the immune system function, yet this aspect is paid very little if any attention by clinicians. The same three factors are indeed object of major attention by clinicians and epidemiologists but for reasons other than their role in the immune defence.

Therefore we thought that a short review of the current knowledge about the possible role of these factors in the innate and the acquired immunity defence system and the potential effects of the related nutritional inadequacies would be warranted under the present circumstances [3–5]. Before considering the specific role of each of these factors and referring the reader to other appropriate sources for more extensive and specialist description [6], we recall here that the innate immunity comprises *i)* the mechanisms of primary defence of our organism against external pathogens (bacteria, viruses, fungi), including the integrity of the skin and of the mucous barriers, and *ii)* the components of the more advanced defence against the same pathogens, once they should overcome these barriers, based on the activity of circulating monocytes and their transformation into macrophages, the cellular elements that will attack and try to block the invasion. The acquired immunity is instead based on the proliferation and balanced differentiation of lymphocytes into B cells, which are primarily intended for the production of circulating antibodies, and T cells, which differentiate into different subtypes producing different cytokines, molecules involved in the inflammatory response to pathogens, some of which increase the power of the inflammatory response whereas others tend to modulate and possibly attenuate it.

Vitamin D

Vitamin D is mainly synthesised in the skin under the influence of ultraviolet (UV)-B light. In addition, a small amount is obtained from the diet through a few food sources, such as oily fish, egg yolk and vitamin D fortified dairy products. After its production or ingestion with food, it gives rise to a complex biological system comprising hormone precursors, active metabolites, carriers, enzymes, and receptors involved in genomic and non-genomic effects. This system has been shown to activate multiple molecular mediators and elicit many physiological functions, which are associated with glucose homeostasis, blood pressure regulation, inflammation, and cancer [7]. In particular, vitamin D has long been known to participate in the activity of the immune system through its active form, 1–25 dihydroxycalciferol (calcitriol). The vitamin D receptor (VDR) is present in both B and T cells and vitamin D was shown to modulate the proliferation, differentiation and inhibition of these same cells [8]. While initially vitamin D was considered basically an immunosuppressive agent, more recently it has rather been thought to play a modulating role in tolerance and homeostasis, mainly based on animal experimental and in vitro studies [9,10], but also with some evidence in humans [11,12]. Evidence has been produced of favourable actions of vitamin D both in terms of innate and of acquired immunity. Although the role of the vitamin D on neutrophil activity is still poorly understood, there is evidence that these cells have the VDR on their surface and that exogenously administered calcitriol reduces their production of inflammatory mediators and formation of reactive oxygen species [13]. Exposure to 1,25(OH)2D3 enhances the differentiation of macrophages from monocytes and induces autophagy, phagosomal maturation and the production of antimicrobial peptides such as cathelicidins [14] for the intracellular killing of bacteria like *Mycobacterium tuberculosis*. Furthermore, the vitamin active metabolite can reduce the production of proinflammatory mediators from M1 macrophages, e.g. cytokines IL-1b, IL-6, IL-12p40, tumor necrosis factor [TNF]-a) and chemokines [15]. We have learned that one of the elements responsible of an unfavourable outcome in SARS-COV2 infection is an excess of inflammatory response, due to a defect in modulation of the response itself [16,17]: vitamin D could exert an important action in this regard, having the ability to direct the immune response toward a reduction in the production of pro-inflammatory cytokines, while favouring the differentiation of T cells towards the production of subtypes that substantially modulate and attenuate the extent of inflammation [18,19]. The benefits of normal vitamin D status against Sars-Cov-2 infection might go actually beyond its immunomodulatory function, involving the preservation of the integrity of the pulmonary epithelial barrier, the stimulation of epithelial repair

and an antithrombotic effect which is conceivably related to its anti-inflammatory action [20].

More recently, some authors assessed the relationship between Covid-19 disease and vitamin D deficiency. The results of these studies are summarised in Table 1.

The issue of vitamin D and immune defence is clinically and epidemiologically relevant given the documented widespread deficiency or insufficiency of vitamin D in the population, particularly among institutionalized elderly people [26]. The impact of vitamin D on the regulation of the inflammatory process is of particular importance in older adults, in obese people and in all those with chronic inflammatory conditions who may be susceptible to a heightened immune response. In these population groups, which were the preferred target of the Coronavirus in its 2020 winter and spring outbreak, hypovitaminosis D is often associated with skeletal demineralization and involves a greater risk of falls and bone fractures [27]. It is thus widely recognized that diagnostic screening and correction of hypovitaminosis D is indicated in the elderly population in relation to the health and functionality of the skeletal and muscular system [28]: albeit in the absence of randomized controlled trial evidence, it is conceivable that this type of intervention may also benefit the immune system functionality.

Table 1 Main findings of studies which assessed the relationship between Covid-19 and Vitamin D deficiency.

Author	Main results
Maghbooli et al. PLOS ONE, 2020 [21]	In 235 hospitalised patients vitamin D sufficiency was statistically associated with a lower risk of unconsciousness ($p = 0.03$) and hypoxia ($p = 0.004$), a lower C-reactive protein blood level ($p = 0.01$) and a higher blood lymphocyte percentage ($p = 0.03$). Moreover, in a logistic regression model, vitamin D sufficiency was independently associated with decreased disease severity.
Entrenas Castillo et al. J Steroid Biochem and Mol Biol, 2020 [22]	Among 76 hospitalised patients (50 with and 26 without Calcifediol treatment) 98% of the patients on calcifediol did not require Intensive Care Unit versus only 50% of the patients not treated with Calcifediol ($p < 0.001$).
Ilie et al. Aging Clin. Exp. Res, 2020 [23]	In European countries: a) inverse correlation between average vitamin D level and number of COVID-19 cases per million population $r = -0.44$; $p = 0.050$]; b) inverse correlation between average vitamin D level and number of COVID-19 related deaths per million, $r = -0.43$; $p = 0.050$).
D'Avolio et al. Nutrients, 2020 [24]	By retrospective analysis of 107 patients undergoing a nasopharyngeal swab with PCR analysis for SARS-CoV-2 and concomitant serum 25(OH)D measurement, lower 25(OH)D levels (11.1 ng/mL) were found in patients positive to SARS-CoV-2 compared with negative patients (24.6 ng/mL), $p = 0.004$).
Panagiotou, Clinical Endocrinology, 2020 [25]	The analysis of 134 Covid-19 hospitalised patients showed that 66.4% were vitamin D insufficient and 37.3% were vitamin D deficient (21.6% severely deficient). Moreover, patients admitted to Intensive Therapy Unit (ITU) had a lower 25(OH)D level compared with non-ITU patients despite being younger ($p = 0.02$).

Sodium

The harmful effects of excess salt intake on the cardiovascular system [29] are paid justified attention, but little or no attention has been given so far to its potential effects onto the immune system activity. Indeed, in the last 10 years increasing evidence has accumulated about the role that sodium plays at this level and about the possible consequences of excess salt intake in this respect [30]. It is now known that the skin represents a site of significant sodium accumulation, sodium being linked to glycosaminoglycans in the extracellular matrix, in the absence of an equivalent amount of water, thus in a condition of local hyperosmolarity [31]. It was also found that a high dietary salt intake induces a greater accumulation of sodium in the skin and also in other sites which are at the "frontier" of our immune defence system, i.e. the gut and the kidney [32,33]. It has been shown that inflammatory states favour an increase in salinity, and that hypersalinity, in turn, attracts macrophages and induces their preferential differentiation into "pro-inflammatory" phenotypes [34], while inhibiting the function of alternatively activated macrophages (M2 macrophages) which exert a modulatory function on the inflammation process [35]. Overall, this pattern of response is functional to the elimination of external pathogens [36], but also determines a lower representation of cellular phenotypes oriented to the modulation of the inflammatory response with the result, at the skin level, of delaying the healing time of wounds and in general inflammatory lesions [35]. In keeping with these findings, it was also shown that a higher sodium environment increased the expression of proinflammatory while inhibiting the expression of anti-inflammatory genes in human monocyte-derived macrophages [37].

Many studies focused on the effect of salt on T lymphocyte differentiation. Activated T lymphocytes proliferate and differentiate in secondary lymphoid organs into effector cells to enter the circulation and migrate to inflamed tissues, as necessary. Depending on the cytokine microenvironment, they can differentiate into TH1, TH2, TH17 or into regulatory T (Treg) cell subtypes [38]. Several studies suggested that salt promotes the differentiation of T17 cells and, conversely, that treating TH17 cells with salt increased their pathogenicity in terms of production of inflammatory cytokines [39]. On the other hand, Treg cells are known to limit the inflammatory process mediated by TH17 cells [40], but their function is inhibited by hypersalinity [41].

A different but related issue is the effect of excess dietary salt consumption on the intestinal microbiota, which has been recognized as an integral part of our immune

system [42]. It was reported that a salt load in healthy volunteers reduced the abundance of various Lactobacillus species in faecal samples, and this was associated with a rise in the concentration of proinflammatory TH17 cells in the blood [43]. Another study showed that a high salt diet in mice led to the expansion of TH17 cells in the small intestine and to elevated IL-17 levels in the blood [44]. These findings suggest that, by affecting the intestinal microbiota, dietary salt might indirectly influence immune cell function in various tissues and therefore also modulate the inflammatory process [45].

What was said previously for vitamin D applies to sodium as well: although there are no randomized controlled trials demonstrating that reducing salt intake increases the protection against viral infections, the correction of excess salt intake, strongly indicated for the known and proven benefits on the cardiovascular system, may conceivably bring about some benefit with regard to the optimal modulation of the inflammatory response in the case of infection, which may be of particular importance in the Covid-19 pandemic.

Alcohol

The harmful effects of inappropriate consumption of alcoholic beverages on the immune system have been well described, both with regard to a single bout and to the consequences of a chronic abuse of the substance. It was reported that upon a single episode of binge alcohol consumption (with mean peak blood alcohol levels above 130 mg/dL) by human volunteers there was within minutes an initial rise in the number of peripheral blood monocytes and in the LPS-induced TNF-α production: this was followed however in a few hours by a rebound fall in circulating monocytes with an increase in the level of the anti-inflammatory IL-10 [46]. These results are in keeping with those of experiments in rodent models in which the measurement of serum cytokine levels at 2hr distance from the administration of ethanol at a dosage equivalent to the one resulting in loss of consciousness in humans showed a decreased production of the inflammatory cytokines IL-6 and IL-12 and by contrast an increase in the production of IL-10 [47].

In contrast to the inhibitory effects of acute alcohol ingestion, prolonged exposure of peripheral blood monocytes from human subjects to ethanol for several days appears to increase TNF-α production without affecting IL-10 production in response to an appropriate cell stimulation [48,49]. Also, prolonged ethanol ingestion in male mice up-regulated NFκB activation and increased the circulating levels of IL-6 and TNF-α in response to lipopolysaccharide stimulation [50]. Overall, the available evidence suggests that alcohol modulates the function of innate immune cells in a dose and time dependent manner, in such a way that acute high dose exposure inhibits whereas long-term assumption stimulates proinflammatory cytokine production [51]. Alcohol consumption also impacts cell-mediated and humoral immunity. Thus, in humans it appears that alcohol consumption can lower lymphocyte number [52,53]. In addition, alcohol abuse was associated with shifts in T lymphocyte phenotype pattern, with decreased percentage of CD45RA+ "naïve" CD4 and CD8 T cells and an increased percentage of CD45RO+ "memory" subsets, as observed in men who consumed an average 400 g/day of alcohol for approximately 25 years [54,55]. Similarly in mice, chronic consumption of 20% ethanol in water for up to 6 months decreased the percentage of naïve T cells and increased the percentage of memory T cells [56–58]. Accumulation of memory T cells has been associated with increased incidence of chronic inflammatory diseases [59,60] whereas the loss of naïve T cells is expected to interfere with the development of efficacious responses to infection and vaccination [61]. It must be noticed however that these alterations in lymphocyte number and phenotype have been described with massive but not with "moderate" alcohol consumption [62]. Chronic alcohol intake was also found to be associated with alterations in circulating immunoglobulin (Ig) levels and in particular with a trend to dose-dependent higher IgA and IgM production [53,63]. Several studies have examined the effects of alcohol consumption on the host response to infection. Thus, chronic alcohol abuse was found to lead to increased susceptibility to bacterial and viral infections [64] and severity [65] compared with control subjects. The incidence of *M. tuberculosis* infection among alcoholics has been found to be increased [66]. Alcohol use has also been shown to drive disease progression in chronic viral infections such as human immunodeficiency virus (HIV) [67] and Hepatitis C [68]. In addition, the magnitude of antibody response following vaccination toward Hepatitis B virus was lower in alcoholics compared to controls [69]. Again, in contrast to the studies above, moderate alcohol consumption was not associated with reduced immune response to infection and vaccination in various studies [51].

Conclusions

We have analysed vitamin D, salt intake and alcohol consumption, as three nutritional factors playing a role in the proper functioning of the immune system and have discussed their potential impact on the modulation of the immune response to SARS-COV2 infection. Obviously, there is no specific recipe to prevent or contrast the SARS-COV 2 infection on nutritional grounds and there is no RCT demonstration that increased ingestion or supplementation of any given substance will confer protection against the new enemy. It may be convened that the maintenance of an optimal nutritional status through the adherence to the evidence-based nutrition guidelines and the practise of a regular physical activity may help to contrast the disease. In particular, we suggest that special attention to the three nutritional factors we hereby highlighted would be part of a logical approach to a nutritional policy at the time of COVID pandemic. For all of these factors there is a large, yet "circumstantial", evidence of an impact on the immune defence: this warrants in our view particular efforts by the

health authorities to pursue the best possible implementation of the measures useful to correct the related well known nutritional criticisms, i.e. vitamin D deficiency or insufficiency, excess salt intake and inappropriate consumption of alcoholic beverages. The detection of individuals affected or at increased risk of occurrence of these criticisms would enable the preventive application of personalized nutritional guidelines to promote individual health, and, accordingly, to improve population health. We propose that the inappropriate intake of salt and alcohol and the risk of inadequate vitamin D status should be object of screening, in particular in subjects at high mortality risk from SARS-COV 2 infection, such as institutionalised elderly subjects and all those affected by predisposing conditions. Appropriate nutritional and pharmacological strategies must be put in place to help individuals to reach an optimal nutritional state. Any improvement in this regard is expected to translate into great advantages for community health.

Declaration of competing interest

The authors have nothing to disclose.

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