COVID-19 Perfect Storm (Part II): Role of Vitamins as Therapy or Preventive Strategy in Aged People

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IMPACT STATEMENT

1. We certify that this work is novel

2. What this research specifically adds to the literature: It has to be considered that a proper function of Immune System requires the presence of adequate concentrations of several micronutrients, like Vitamin A, D, E and C. However, a large part of population, mainly the elderly individuals, presents important deficiency in these micronutrients. For the first time, we

have postulated the potential role of Vitamins A, D, E and C in interfering with the inappropriate host's inflammatory response caused by SARS-CoV-2 and in attenuating it. In particular, the pathogenesis of autoimmune diseases and their treatment may serve as a paradigm for a better understanding of the mechanisms involved in the development of the Cytokine Release Syndrome (CRS). This life-threatening condition emerges in about 15-20% of patients with SARS-CoV2 and its control is necessary to prevent the fatal outcome in these subjects.

In our paper we indicate the potential targets of Vitamin A, D, E and C in modulating the exhuberant immune response, arising during SARS-CoV-2 infection. This action probably is due to the direct down-regulation in the synthesis, release or function of cytokines (like IL-6, IL-8, IL-17 and TNF-α) or enzymes (like Cyclooxygenase-2 and Lypo-oxygenase) with strong pro-inflammatory activities as well as to the shift of Th17 mediated immune-response towards a T-cell regulatory phenotype, as observed in patients with autoimmune diseases. Taken together these observations provide the rationale for the use of these micronutrients as a part of a multi-treatment strategy against SARS-CoV-2 infection for the therapy of patients with acute forms of infection or as strategy for the improving the Immune System function. This approach could produce a beneficial effect on several groups of population, mainly elderly people, and should be considered in these individuals with preventive purposes. Well-designed trials should be carried out with the aim to confirm or deny this strategy.

ABSTRACT

OBJECTIVES. In December 2019 a novel human-infecting coronavirus, SARS-CoV-2, has emerged. The WHO has stated the epidemic as a "public health emergency of international concern". A dramatic situation has emerged with thousands of deaths, occurring mainly in the aged and very ill people. Epidemiological studies suggest that immune system function is impaired in elderly individuals and these subjects often present a severe deficiency in nutrients as fatsoluble and hydrosoluble vitamins.

DESIGN. In this second part of the review about Cov2 in aged people, we searched for studies describing the possible efficacy of vitamins A, D, E and C in improving the immune system function and their possible activities against viruses.

RESULTS. Vitamins may shift the proinflammatory Th17 mediated immune-response arising in the autoimmune diseases towards a T-cell regulatory phenotype. These diseases may serve as a paradigm for the study of CRS emerging in the course of SARS CoV-2 infection.

CONCLUSION. This review discusses about the possible activity of Vitamin A, D, E and C in restoring normal antiviral Immune System function or the potential therapeutic role of these micronutrients as a part of a multi-treatment strategy against SARS-CoV-2 infection.

Keywords: SARS; CoV-2; COVID-19; vitamins; therapeutic strategy

INTRODUCTION

This review is the second part of a pair. The first one is entitled "**COVID-19 perfect storm (part I): cytokine release syndrome in aged people".**

Novel strategies for the treatment of this pathological condition are urgently required. The pathogenetic mechanisms of SARS-CoV-2, which probably operate in the course of this infection and cause severe forms in about 10-15% of patients suffering from this disease, are represented by the establishment of an exuberant, ineffective and deleterious inflammatory immune response **(see "COVID-19 perfect storm (part I): cytokine release syndrome in aged people").** Briefly, it is characterized, in some subjects, by the Cytokine Release Syndrome with the establishment of a very serious clinical picture, including fever, hypotension, hepatic failure, uremia, acute respiratory distress syndrome. These events probably culminate into the disseminated intravascular coagulation syndrome, with a high mortality rate [1]. On the basis of these assumptions, it may be hypothesized that the treatment of patients with SARS-CoV-2 infection should be started as soon as possible, with the purpose to modulate the proinflammatory response and to prevent the emergence of a deleterious host's immune response [2]. A wide series of studies carried out in autoimmune diseases have suggested that some liposoluble and hydrosoluble vitamins (A, D, E and C) may regulate the immune system activity and attenuate its exuberant activity. Vitamin A, D, E and C, alone or in association and used not as simple supplements, but at as drugs at pharmacological dosages may exert promising anti-inflammatory and immune modulatory effects [3-6].

AIM OF THE REVIEW

On the basis of the available epidemiological data concerning the current outbreak of the novel SARS-CoV-2 in Italy, the infectious disease caused by this virus represents a very severe health problem for individuals over 60, with aged-people at higher risk of severe forms of disease and

of death. About 85% of individuals who died from COVID-19 infection were over the age of 60 (https://www.epicentro.iss.it/, Istituto Superiore Sanità, accessed on 25/3/2020).

Taking advantage from all these epidemiological data, observations, assumptions and hypotheses, we have performed this review to investigate the possible immunoregulatory role of Fatsoluble and Watersoluble vitamins in this life-threatening condition. This strategy may contribute to identify the possible viral targets and to hypothesize a potential therapeutic strategy against this pathogen in a coordinate and consequential way.

RESULTS

The possible activity of liposoluble and hydrosoluble vitamins in the direct and/or indirect modulation of host immune response by vitamins during SARS-CoV-2 infection

Some of the results obtained with the use of vitamins alone or in association with different drugs at pharmacological dosages to counteract both DNA and RNA viruses seem to be encouraging and may provide the rationale for the inclusion of these micronutrients in the multi-therapeutic schedules for the treatment of SARS-CoV-2. In the next parts of the current paper we will examine some of the mechanisms involved in CoV-2 mediated-pathogenesis and we will discuss the potential antiviral activities and the possible viral targets of A, D, E and C vitamins.

These micronutrients have been reported to modulate and regulate: 1) the host-inflammatory status in several chronic diseases [7], including viral infection. It has been shown that vitamin D and Vitamin E, the latter displaying this function mainly in its succinate form, are able to quench reactive oxygen species (ROS) and prevent the activation of a wide series of genes as well as the modification of cytoplasmic enzymatic pathways. Overall, all these components are involved in the induction and control of inflammatory cascade [8, 9]. Furthermore, vitamin C is able to attenuate ROS-mediated injury in some critical cell micro-organelles, like mitochondria, and to confer protection against oxidative-mediated damage [10]. These mediators are released in

the tissue microenvironment, where the inflammatory process originates, following the influx of a wide spectrum of different immune cells. In the initial phase of the inflammation, these reactive oxygen species exert a protective role, counteracting the invading pathogens [11]. However, the continuative production of these mediators is associated with the establishment of a persistent self-maintaining pro-oxidative status with the progressive impairment of a lot of cell functions of micro-organelles, including mitochondria and endoplasmic reticulum. These events lead to a general tissue damage at a microscopic level and are associated with clinical effects of different severity [12]. Overall, the injury involving cell micro-organelles and microenvironment is induced and mediated by the synthesis or by the activation of elements associated with inflammatory cascade, including NF-kB, AP-1 and PGE2. It has been reported that nucleocapsid and spike proteins of SARS-CoV are able to directly up-regulate the promotor of IL-6, IL-8, IL-12, TNF-α, COX-2 and probably IL-17 genes and indirectly of IL-1 α and β via NF-κB and AP-1 pathways **(Figures 1 and 2)** [13, 14]. Studies in vitro have shown that 1α,25-dihydroxyvitamin D3 is able to down-regulate DNA Binding of Nuclear factor-kappaB (NF-κB) to promoters of IL-6, IL-8, IL-12 and COX-2, leading to moderate transcriptional repression with decreased synthesis of all these interleukins and COX-2 [15-17]**.** NF-κB motifs have been observed even in IL-1 α and β [18] and IL-17 [19], and it is conceivable that 1α,25-dihydroxyvitamin D3 may also down-regulate the synthesis of these interleukins, although no studies concerning this topic are available. It has been shown that vitamin E is also able to inhibit NF-κB binding activity [20, 21]. Therefore, these micronutrients may down-regulate the synthesis of IL-6, IL-8, IL-12 and COX-2. A significant anti-inflammatory effect of all-trans-retinoic acid (ATRA) on proinflammatory cytokine and chemokine production in adipocyte and adipose tissue model has been observed in models of human and mouse adipocytes, via inhibition of NF-κB [22]**.** Overall, the use of vitamin A, D, E and C might contribute to decrease the exuberant inflammation, which is observed during the development of severe forms of SARS-CoV-2 infection and to attenuate

the Cytokine Release Syndrome. It is not known whether the supplementation of CoV-2 patients with these vitamins at pharmacological dosages, alone or in combination with different associations, might induce the significant inhibitory effects on the synthesis of the above-mentioned interleukins. Well-designed trials are needed with the purpose to clarify this hypothesis.

2) The normal activity of Immune Response both in its innate and adaptive arms. An in-depth discussion about the regulatory role of the Vitamin A, D, E and C vitamins in the proper functioning of Immune System against pathogens is beyond the scope of this article. Therefore, we will present in brief our current understanding of the essential activities of each vitamin in modulating a broad range of Immune processes and regulate Immune response against pathogens. The coordinate cooperation of all these micronutrients is essential for the maintenance of an adequate homeostasis and a proper activity of Immune System.

Vitamin D

The 1,25(OH)2VD3 acts on T cells down-regulating T-helper-1 (TH1)-cell cytokines, particularly IFNγ, and stimulating TH2-cell responses [23, 24]. This event is induced by the decrease of IFNγ release and by the enhancement of IL-4 production [25]. Furthermore, 1,25(OH)2 VD3 regulates effector T-cell differentiation by means of modulation of antigen-presenting DCs, in which it decreases the synthesis of IL-12, a cytokine that promotes TH1-cell responses [15, 26]. 1,25(OH)2VD3 also exerts a main effect in immune system activity, by counteracting TH17-cell responses and differentiation of uncommissioned TH 0 cells to TH 17 compartment, as this micronutrient is able in part to down-regulate several pro-inflammatory cytokines, including IL-6, IL-17 and IL-23 production [27, 28], and promotes the reciprocal differentiation and proliferation of forkhead box protein 3 (FOXP3)+ regulatory T (TReg) cells [29, 30]**.** Furthermore, 1,25(OH)2VD3 decreases B-cell expansion, plasma-cell development and IgG secretion [31]**,**

probably modulating the activities of antigen presenting-cell (APC) and by a means of a direct action on B cells [32]. In addition, 1,25(OH)2VD3 decreases the synthesis of IL-12 and simultaneously increases the production of IL-10 by DCs. Therefore, the TH1-cell response is shifted to a T regulatory type 1 (TR1) cell response. The results emerging from these experimental studies in patients with Rheumatoid Arthritis have provided the rationale for the use of 1,25(OH)2VD3 in association with other drugs [3], including the anti-IL-6 receptor monoclonal antibody (Tocilizumab), in the treatment of patients suffering from Rheumatoid Arthritis with different severity [5]**.** Interestingly, the best response (assessed by means of Diseases Activity Scores) to the therapy was obtained in patients with sufficient serum 25(OH)D levels (≥ 30 ng/mL) when tocilizumab was initiated, in comparison with patients with lower serum 25(OH)D levels (< 30 ng/mL). 1,25(OH)2VD3 primarily exhibits inhibitory activities on the adaptive immune response. However, in some circumstances, it may enhance the release of both IL-1 by monocytes and macrophages. Vitamin D is able to stimulate intracellular type I IFN system which exerts antiviral activities [33].

Vitamin A (Retinoic Acid)

The term vitamin A indicates both retinol and its analogues, called retinoids, of which at least 1,500 different types are known, between natural and synthetic [34]. Carotenoids that contain at least one unsubstituted β-ionone ring (such as beta-carotene) are also considered to be precursors of vitamin A [35]. According to available data, Vitamin A and its metabolites are able to regulate both innate and adaptive arms of immune response, increasing IL-2 secretion and to modulate proliferation, differentiation and signaling as well as cytokine production [36]**,** both in T, B and antigen-presenting cells [34, 37]. Vitamin A metabolites also modulate more specific functional aspects of the immune response, such as the TH1–TH2-cell balance and the differentiation of TReg cells and TH17 cells. In particular, depending on the physical and biochemical

composition of the microenvironment, Vitamin A in presence of different concentration of cytokines and transcription factors stimulates TH 0 cells to assume a TH-2 phenotype [38], whereas inhibit TH-1 subtypes. Furthermore, in presence of adequate concentration of transforming growth factor-β (TGFβ), retinoic acid promotes TReg-cell differentiation in peripheral tissues, whereas inhibit the progression of lymphocytes from TH0 to pro-inflammatory TH-17 [39-41]**.** Retinoic acid displays gut imprinting ability on T and B cells and induces the differentiation of B cells to plasma-cells IgA productions. A severe defect in intestinal immune responses [42] with enhanced mortality is detectable in patients with Vitamin A deficiency. These subjects suffer from gastrointestinal and respiratory infections [43, 44]**.** On the other hand, Vitamin A administration is associated with a significant reduction in diarrhea and mortality in children with HIV infection or or malnourishment [45]. Moreover, Vitamin A is able to stimulate intracellular type I IFN system which exerts antiviral activities [46].

Vitamin E

Vitamin E represents a strong lipid-soluble compound with antioxidant properties and it is detectable in elevated amounts in immune cells [47]. Scavenger activity is one of the most important action of Vitamin E, but this characteristic is not able to explain overall effects of this nutrient, as eight members in the vitamin E group (α-, β-, γ-, and δ-tocopherols and α-, β-, γ-, and δ-tocotrienols) exist in nature, with almost equal ability to quench free radicals. Each of these different forms of Vitamin E sometimes exerts distinct from the other analogues and not completely predictable activities [48]. Vitamin E may interact with several classes of enzymes, modulate their binding abilities to the plasma membrane and modify a large series of cell signalling pathways. The Families of enzymes modulated by Vitamin E are represented by: Protein kinases, Protein phosphatases, Lipid kinases, Lipid phosphatases, Lipid metabolic enzymes and enzymes involved in cAMP (cyclic Adenosin monophosphate) metabolism. They regulate a wide spectrum of key cell processes, including energy production, proliferation/apoptosis/death, protein synthesis, maintenance of quiescent status. A lot of these enzymes are involved in crucial activities of immune systems and in the inflammatory events, like Cyclooxygenase-2 (COX-2), Phospholipase A2 (PLA2), 5-, 12-, and 15-lipoxygenases (5-, 12-, 15-LOX), Protein kinase C (PKC), Protein kinase B (PKB/Akt), Protein tyrosine kinases (PTKs). A wider discussion about all these aspects is beyond the aims of this paper and will not be carried on further, but it has to be underlined the key role of Vitamin E in the regulation of the inflammatory process [49]. Vitamin E and its metabolites have been shown to attenuate and limit inflammation by directly targeting COX-2 and 5-lipoxygenase [50]. This micronutrient displays additional functions as effective regulator of the immune activity. Vitamin E supplementation above current dietary recommendations increases the activity of the immune system, confers protection against several pathogens and decreases the risk of infection, mainly in aged subjects [51]. Some cell-based, pre-clinical and clinical studies have evaluated the effects of vitamin E on the immune

system functions and inflammation [52-54]. The most important effects of Vitamin E supplementation on immune system activities include: lymphocyte proliferation, after mitogenic stimulation, increase of delayed type hypersensitivity (DTH) response, via stimulation of IL-2 production, decrease of PGE2 via COX-2 inhibition and reduction of IL-6 release [55]. Furthermore, in both in vitro and in vivo studies Vitamin E has been shown to improve Natural-Killer, naive T-lymphocytes and dendritic cell activities, to promote initiation of T cell activation signals as well as to rebalance IL-12 production and Th1/Th2 ratio. Furthermore, Vitamin E inhibits the production of pro-inflammatory cytokines, including IL-1, IL-6, TNF and the chemokine IL-8, by monocytes and macrophages. Vitamin E is able to stimulate intracellular type I IFN system which exerts antiviral activities [56-62].

Vitamin C

Vitamin C also exerts a regulatory effect on immune system function, in particular it has been reported to modulate the T cells activities of adaptive arm. Some studies have shown that vitamin C decreases mRNA expression of proinflammatory cytokines in vitro or inflammatory status in obese patients with hypertension in vivo. Dietary supplementation in these subjects reduced serum levels of high-sensitivity C-reactive protein, interleukin 6 (IL-6), fasting blood glucose (FBG) and triglyceride (TG) after 8 weeks of treatment [63]**.** In addition, the combined supplementation with Vitamin C and E has been associated with the decrease of oxidative stress in patients with HIV infection and with a trend towards a reduction in viral load [64]. Furthermore, Vitamin C supplementation alone or in association with Vitamin (transretinoic acid) A is able to generate stable antigen-specific regulatory T cells in animal models of autoimmune- or acute graft versus host-diseases [65, 66]. Favorable effects of Vitamin C in alleviating the common cold as well as against pneumonia have been reported in some controlled trials. Vitamin C is able to stimulate intracellular type I IFN system which exerts antiviral activities. Additional studies are needed to confirm the encouraging role of Vitamin C in the treatment of patients with infections, caused by bacteria, viruses, and protozoa [67].

CONCLUSION

The lesson emerging from all these considerations, assumptions, and available data is that the different forms and metabolites of fatsoluble and hydrosoluble vitamins constitute a very complex mixture with multiple actions. Therefore, their activities should be not considered individually, but as a whole, taking into account that the final effect of each vitamin alone or in combination with the other micronutrients depends on the remodulation and on the rebalancing of the overall activities of the Immune System and are not directly predictable. Therefore, a key

general point emerges: fatsoluble and watersoluble vitamins possess pleiotropic regulatory effects on a large series of cell activities and represent powerful means of modulating and modifying various crucial functions of the cells. On the basis of all these considerations it seems reasonable to hypothesize the use of Vitamin A, D, E and C with preventive purpose, with the aim to restore the Immune System function in aged people at increased risk of infection-related mortality as well as for the treatment of patients suffering from SARS-CoV2-mediated acute infection [68]. Taking advantage from all these immunopathogenic assumptions as well as epidemiological and clinical observations, a possible useful approach for the effective management of the health concern induced by SARS-CoV-2 should include the subdivision of the general people into two groups: 1) Patients with acute infectious disease, requiring an effective antiviral treatment. The therapeutic schedule for these patients may include: a) antiviral therapy with the current available drugs with the reported effective antiviral effects in preliminary trials and studies. It may be hypothesized that this treatment should be administered as soon as possible to block viral replication as well as synthesis and release of viral proteins (mainly nucleocapsid and spike proteins) with the purpose to prevent the establishment of a self-maintaining and self-increasing robust pro-inflammatory loop, leading to the "cytokine release syndrome" in the first phases of the disease; b) immunomodulatory therapy, including: i) monoclonal antibodies against IL-6 receptor (as proposed in very preliminary studies) and eventually against IL-1 and/or IL-8, as well as cyclo-oxigenase inhibitors, such as aspirin or FANS with the purpose to block or to prevent the strong inflammatory response and the release of further cytokines and mediators of inflammation. This approach should be also started as soon as possible. Unfortunately, no trials investigating the efficacy and safety of this treatment as well as its optimal duration are available; ii) therapeutic schedules including the administration of liposoluble and hydrosoluble vitamins (such as A, D, E and C) on the basis of

the well-known beneficial immunoregulatory and immunomodulatory roles of these micronutrients.

2) General population without SARS-CoV-2-related acute infection, including healthy or young individuals as well as aged-people or patients with chronic diseases. Epidemiological data show that elderly- or persistently ill subjects are at a higher risk of death, following SARS-CoV-2 infection, in comparison with younger or healthier individuals. Furthermore, the available studies report that Fatsoluble and Hydrosoluble vitamins are necessary for the correct function of the Immune System, whereas patients with different chronic infections, including HBV, HCV and HIV infections, vitamin A, D, E and C deficiency is associated with higher levels of viral replication and with higher titres of inflammatory cytokines, like IL-6 and TNF-α. Therefore, the supplementation of these classes of individuals with A, D, E and C vitamins may represent a possible preventive strategy with the aim to improve Immune System function. The above-mentioned micronutrients possess well-known multiple nuclear and cytoplasmic targets in all the different types of mammalian cells, and they may modulate and regulate an elevated number of intra- and extracellular- pathways. Therefore, these vitamins may contribute to remodulate and to restore the immune system functions and to prevent the cytokine release syndrome. Overall, these compounds may be considered not only as physiological substances but also as real drugs with potential useful or dangerous effects. Unfortunately, to date no studies have assessed the blood concentration of these liposoluble vitamins in patients with SARS-CoV-2 as well as it is unknown whether a vitamin deficiency may be associated with a more severe course and outcome of this disease. Therefore, trials evaluating blood concentration of these compounds should be performed as soon as possible. Taking into account all these data and the possible side effects of these compounds, a dosage of blood liposoluble vitamins should be performed in patients with SARS-CoV 2 infection already in the early phases of disease.

Unfortunately, no studies have been designed to verify the real usefulness of this potential preventive strategy and the possible really effective dosages for each of these vitamins.

A lot of trials have been conducted so far with the aim to assess the usefulness of Vitamins A, D, E and C for the treatment of patients with viral infectious diseases or of individuals with autoimmune diseases, like Rheumatoid Arthritis and Lupus Erytematosus Systemicus or patients with infectious diseases. To the best of our knowledge, the Vitamin A, D, A and C, at the dosage used, have been demonstrated to possess safe profiles with no important side-effects in relation to the potential therapeutic effects. Therefore, a possible use of these micronutrients might be considered in a multi-therapeutic regimen of treatment.

Furthermore, it must be underlined that about 20% of patients with CoV-2 infectious disease develop an interstitial pneumonia with severe tissue damage. It is unclear whether patients who recover from infection will have a complete resolution of lung injury with the full restoration of tissue integrity or a persistent damage will develop with the possible evolution to a fibrotic tissue reaction and with the consequent emergence of a disability status in these patients. Vitamin D and A have resulted to be trophic for alveolar epithelial cells in in vitro studies, whereas Vitamin C has not obtained significant results in decreasing alveolar damage in a randomized, double-blind, placebo-controlled, multicenter trial in comparison with placebo in patients with Sepsis and Severe Acute Respiratory Failure [69]. Overall, all these micronutrients may have a possible role in the mechanisms of alveolar tissue repair and their potential activities should be evaluated in future trials [70, 71].

In conclusion, in this article and in previous one ("**COVID-19 perfect storm (part i): cytokine release syndrome in aged people**") we have provided an evaluation of the available data concerning this very life-threatening disease worldwide, known as SARS-CoV2, then we have examined the crucial mechanisms potentially involved in the development of this severe illness.

On the basis of our research we have identified the possible viral and host cell targets and suggested a rationale for poly-therapeutic approaches. Further studies are strongly required to increase our knowledge in the immunopathogenesis of this disease, with the aim to contribute to the control of this public health emergency.

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FIGURE LEGENDS

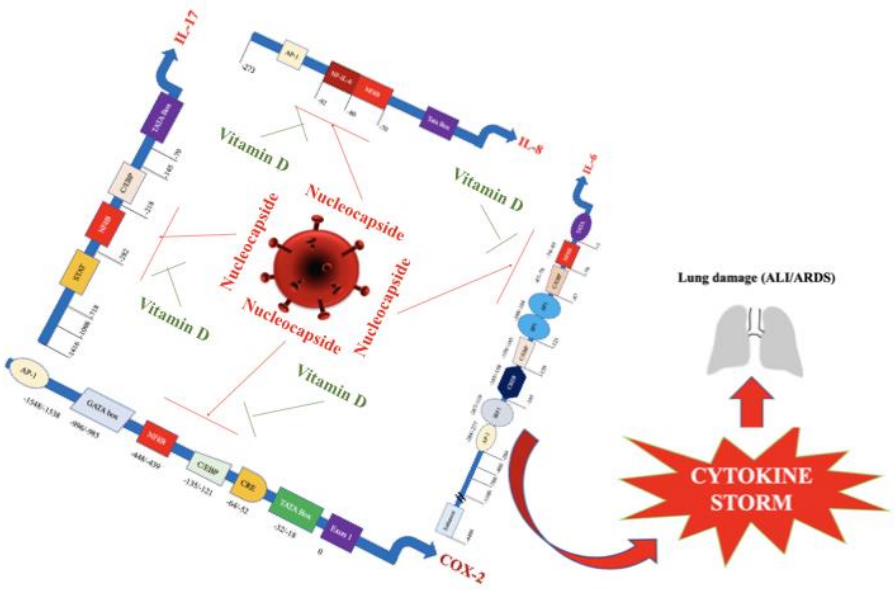

Figure 1. Possible pathogenetic mechanisms involved in Cytokine Syndrome Release in patients with SARS-CoV-2 infection. SARS-coronavirus nucleocapsid and/or spike viral proteins may directly bind to DNA specific motifs (nuclear factor-kappa B or NF-kB and

CCAAT/enhancer binding protein or C/EBP) on the promoters of a wide series of genes encoding proinflammatory cytokines or may interact with specific subdomains in NF-kB protein and activate it. NF-kB is one of the main mediators involved in the generation of the inflammatory process. Therefore, nucleocapsid and/or spike viral proteins may directly or indirectly induce the synthesis of IL-1, IL-6, IL-8, IL-17 and TNF-α during the development of SARS-CoV-2-caused infection. It is conceivable that viral replication rate in infected cells progressively increases, during SARS-CoV-2 infection. This event may be associated with the release of elevated amounts of N and S proteins. The high load of these antigens binding to the promoters of the proinflammatory cytokines and enzymes may induce a hyper-activation in the transduction and translation of these genes. Therefore, elevated amounts of proinflammatory cytokines are produced and released. The massive secretion of these mediators is associated with the emergence of the Cytokine Release Syndrome. Aged-people suffering from chronic diseases and with the impairment in the immune system function are at high risk of a severe pathological disease. The final effect of these events is the induction of a proinflammatory pattern leading to a self-maintaining loop with the possible progressive impairment of clinical conditions. Vitamin A, D; E may decrease the binding of NF-κB to their DNA specific sequences and reduce pro-inflammatory cytokine synthesis, preventing or attenuating the establishment of the Cytokine Release Syndrome.

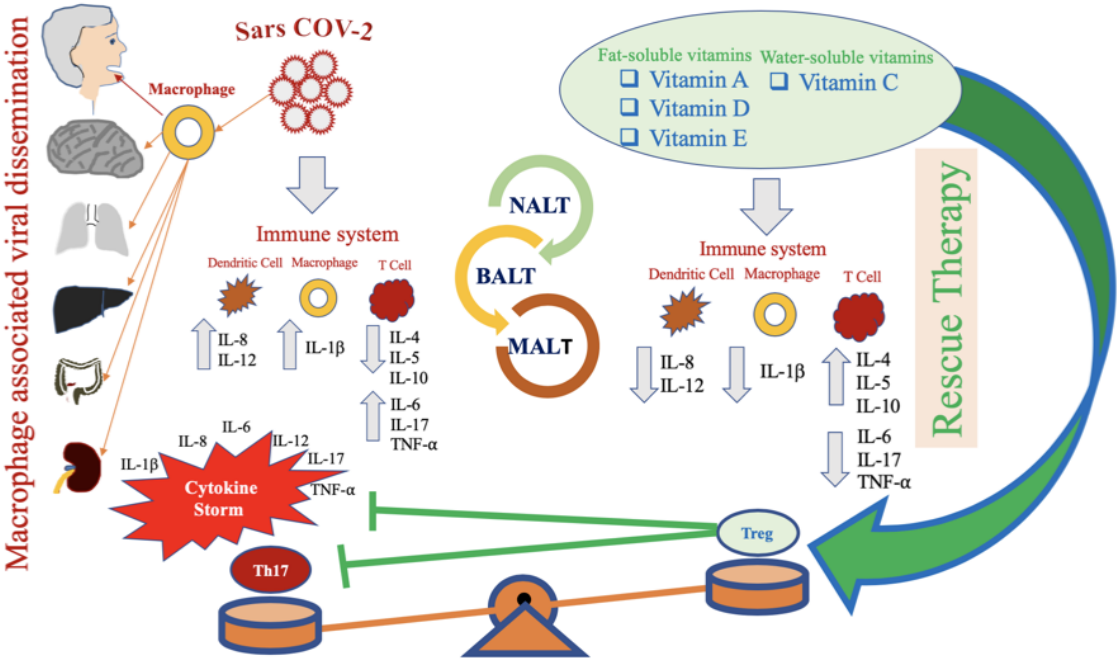

Figure 2. Possible pathogenesis in SARS-CoV-2 infection. Virus infects the human respiratory tract, entering the epithelial cells of the trachea, bronchi, bronchioles, lungs, as well as it colonizes also resident, infiltrating, and circulating cells of Immune System. Following this event, the virus spreads to cells of different organs, including the mucosa of the intestine, the epithelium of the renal distal tubules, the neurons of the brain via infected circulating immune cells. The wide colonization of the various organs contributes to explain the variety of symptoms. Based on this assumption, it may be hypothesized that infected circulating immune cells reach the nasal-associated lymphoid tissue (NALT), the mucosa-associated lymphoid tissue (MALT) and the Bronchus-associated lymphoid tissue (BALT). The Immune System function is severely impaired and a pneumonia with different degrees of severity may emerge in infected individuals with possible fatal outcome. These subjects generally develop more severe clinical pictures and present a more elevated mortality in comparison with healthy subjects. Since several years ago, epidemiological studies have underlined that the elderly-

people as well as the individuals with chronic diseases often present a compromised immune function even in normal situations and in times of non-medical-emergency. These individuals have a lower serum concentration of fatsoluble and hydrosoluble vitamins. Itis well-known that these micronutrients play a crucial role for the normal function of Immune System. A, D, E and C vitamins, used not as simple supplements, but at pharmacological dosages may have a significative impact in counteracting the immune-suppressive activity of SARS-CoV-2 and may may attenuate several aspects of the host's exuberant immune response against this pathogen. In particular CoV-2 may promote a shift of immune response towards a Th17 proinflammatory phenotype, causing the development of an unfavorable clinical evolution of the disease. Taking advantage from studies performed in patients with autoimmune diseases, like Rheumatoid Arthritis and LES, it is conceivable that the promotion of an anti-inflammatory response, mediated by the induction of a prevalent T regulatory-cell phenotype may represent a very promising strategy for the treatment of the patients suffering from the CoV-2-related infectious disease.