



The Long History of Vitamin C: From Prevention of the Common Cold to Potential Aid in the Treatment of COVID-19

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From Pauling's theories to the present, considerable understanding has been acquired of both the physiological role of vitamin C and of the impact of vitamin C supplementation on the health. Although it is well known that a balanced diet which satisfies the daily intake of vitamin C positively affects the immune system and reduces susceptibility to infections, available data do not support the theory that oral vitamin C supplements boost immunity. No current clinical recommendations support the possibility of significantly decreasing the risk of respiratory infections by using high-dose supplements of vitamin C in a well-nourished general population. Only in restricted subgroups (e.g., athletes or the military) and in subjects with a low plasma vitamin C concentration a supplementation may be justified. Furthermore, in categories at high risk of infection (i.e., the obese, diabetics, the elderly, etc.), a vitamin C supplementation can modulate inflammation, with potential positive effects on immune response to infections. The impact of an extra oral intake of vitamin C on the duration of a cold and the prevention or treatment of pneumonia is still questioned, while, based on critical illness studies, vitamin C infusion has recently been hypothesized as a treatment for COVID-19 hospitalized patients. In this review, we focused on the effects of vitamin C on immune function, summarizing the most relevant studies from the prevention and treatment of common respiratory diseases to the use of vitamin C in critical illness conditions, with the aim of clarifying its potential application during an acute SARS-CoV2 infection.

Keywords: vitamin C supplementation, viral infections, COVID-19, pneumonia, immune function, athletes, non-communicable diseases, frail elderly subjects

INTRODUCTION

Vitamin C (ascorbic acid) plays an important role in the normal functioning of the immune system (1–4) and its use in preventing and/or treating infections has strongly attracted the interest of physicians and investigators for almost a century. A plethora of papers have been published on this topic, but, although it is well known that a deficiency of vitamin C due to a low nutritional intake leads to a greater susceptibility to infections (5), the possibility of reducing the incidence of viral diseases in a well-nourished population through the use of dietary supplements based on vitamin C is not adequately supported in literature. At present, very little evidence supports the benefit of high doses of vitamin C supplementation on immune function in healthy individuals (4, 6) and several authors have underlined that this practice is ineffective in preventing the common cold and viral infections in most subjects (7–12). Despite this, the popular belief that an extra intake of vitamin C can boost the immune system is still widespread and every year the market claims that the use of supplements is a winter remedy to prevent infectious disease.

While scientists' current position is not to recommend the use of vitamin C supplementation to prevent viral invasions in healthy subjects, more promising—though questioned—data seem instead to emerge from the intravenous administration (IA) of this vitamin in acute respiratory conditions or critical illnesses. Furthermore a potential pharmacological role during early phases of the new coronavirus (SARS-CoV2) infection and its related disease (COVID-19) was recently put forward (13–18). The rapid worldwide spread of SARS-CoV2 and the consequent pandemic emergency recognized by World Health Organization urgently requires a global effort to identify anything that can treat symptoms and reduce deaths. At the beginning of June, more than 6,600,000 cases of infection and 391,000 deaths related to COVID-19 had been reported globally and the number of cases is constantly increasing worldwide (19). Currently, no specific antiviral therapy has been approved for the cure of COVID-19 (20), and this has led researchers to speculate on a possible adjuvant treatment based on indirect evidence from severely ill patients and patients with sepsis conditions (21). Sepsis is a life-threatening organ dysfunction caused by an impaired host response to infection, characterized by a dramatic failure of the circulatory, metabolic, and immune systems, and recognized as the primary cause of death from infection: patients who develop septic shock can have hospital mortality rates of up to 50% (22). On these clinical conditions literature shows that high doses of vitamin C by intravenous infusion may reduce the inflammatory cytokine-related production and potentially improve important outcomes such as the duration of mechanical ventilation time and mortality rates (13–18). This is of particular importance since acute respiratory distress syndrome (ARDS) is one of the most frequent severe conditions registered in COVID-19 patients (23). ARDS is a serious and, in some cases fatal, syndrome characterized by a strong inflammatory response with massive alveolar damage and multiple organ failure,

requiring intensive care unit (ICU) treatment (24). Authors reported a percentage of ARDS cases of around 15% among hospitalized patients with SARS-CoV2 infection (25).

Data on the use of intravenous-administered vitamin C in COVID-19 patients are still unavailable, but clinical trials to explore the efficacy of this treatment are currently in progress in several countries (26) and important results will be available soon.

Based on the above, the aim of this review is firstly to summarize the immunological role of vitamin C with a description of its potential effects as a dietary supplement, on the mechanisms involved during respiratory viral infections, and in relation to the inflammatory response considering different subject categories and clinical conditions; secondly, the manuscript describes the updated literature on the IA of vitamin C in the treatment of severe sepsis and ARDS conditions, with the aim of establishing whether the current clinical background on this topic offers strong enough perspectives to propose vitamin C for a pharmacological application to reduce the dramatic cytokine production and regulate other recognized COVID-19-related immune responses.

PHYSIOLOGY OF VITAMIN C

Bioavailability

Vitamin C is an essential nutrient that must be taken through the diet as humans are unable to synthesize it (27). Thus, our body has developed an effective adaptation system which maintains the organic reserves of vitamin C and prevents its deficiency due to a low dietary intake. These adaptations include a higher absorption and recycling capacity of vitamin C compared to other animal species (e.g., goat and reptiles), which can normally produce it (28, 29). Animal studies have shown that vitamin C is preferentially stored in the brain, adrenal gland, liver and lungs (30–33) but its levels in these organs are rapidly depleted after about one week of dietary insufficiency (31). In humans, skeletal muscle represents the major pool of vitamin C (34). Muscle fibers also lose vitamin C content very rapidly under inadequate dietary intake. However, a consumption of half a kiwifruit per day seems to be enough to saturate the muscle tissue's vitamin C concentrations in non-smoking men (35). Vitamin C homeostasis is finely regulated by at least four mechanisms: intestinal absorption, transport to tissue, renal reuptake, and urine excretion, mainly regulated by a family of proteins named Sodium-Dependent Vitamin C Transporters (SVCT) (36). Considering the individual variability in healthy subjects, studies suggest that a daily intake of vitamin C from 100 to 400 mg ensures 100% of the bioavailability and blood saturation with a steady state of plasma concentration that reaches a maximum level of approximately 70–80 $\mu\text{mol/L}$ (37, 38). Generally, if the intake of vitamin C exceeds 500 mg/day, a further increase in plasma concentration is inhibited and the bioavailability can decrease close to 30% when more than 1,000 mg of vitamin C is administered in a single bout (39). This occurs because when 500–1,000 mg of vitamin C is administered orally, the intestinal transporter (SVCT1) rapidly achieves its maximal

saturation, while the urine excretion of the vitamin is progressively increased (38, 39). The measure of plasma vitamin C concentration may be considered, even though the circulating values cannot be used as a reliable marker of the body stores (about 5 g) (40). A plasma concentration value of vitamin C lower than 23 $\mu\text{mol/L}$ reflects a depletion of the vitamin C pool (state of hypovitaminosis), while clinical symptoms of scurvy occur when plasma values are lower than 11 $\mu\text{mol/L}$ (41).

Recommended Dietary Allowances

To maintain adequate body stores, recommended dietary allowance (RDA) for vitamin C has been proposed over the years. The RDAs vary among countries: e.g., current recommendations in the United States and Canada is 90 mg/day for adult men and 75 mg/day for adult women (42), while in Italy the suggested intakes are 105 mg/day and 85 mg/day for adult men and women, respectively (43). This variation in RDAs can be explained by the different criteria used by various authorities to define the estimated average requirement (EAR) for vitamin C, including prevention of scurvy, immune cell support, maintenance of an adequate plasma vitamin C level, and optimizing health (44). Furthermore, RDAs vary among subjects as several factors can modify vitamin C requirements, including gender, age, smoking, pregnancy, and lactation (44).

Several authors and guidelines indicated that males need more vitamin C than females (45–51) probably due to the higher body weight and fat-free mass of men compared to women (52).

In children and adolescents the RDAs for vitamin C are generally derived from adult needs and adjusted in relation to their lower body mass (46, 47, 53) as reported by Carr and Lykkesfeldt (44). In Italy, for example, SINU recommends an intake of 45 mg for children from 4 to 6 years of age (45). Epidemiological studies indicate that a lower vitamin C status can be found in the elderly, suggesting that they require a higher intake compared to adults (54–56). However, currently only France has developed specific guidelines for subjects from 75 years of age, indicating a daily intake of 120 mg (57).

Vitamin C requirements are higher in women during pregnancy (44): the hemodilution due to the increase of blood volume and the active absorption of vitamin C by the fetus during its development lead to a reduction of the vitamin status (58). Even lactation increases the vitamin C requirement of women, to satisfy the vitamin needs of the infant normal growth. Most countries recommend an extra daily intake of 10–20 mg for pregnant women and an extra daily intake of 20–60 mg/day for women during lactation (44).

Smokers usually have lower plasma values than non-smokers, probably due to increased oxidative stress and higher turnover of vitamin C. In addition to this, a reduced vitamin C status in smokers is also due to the dietary intake of vitamin C, which is usually lower compared to non-smokers (59). Therefore, in order to compensate these conditions, authorities have recommended an additional intake of 20 to 80 mg/day of vitamin C for these subjects, setting the RDAs for smokers at 120–155 mg/day (44).

Some other factors have been recognized as reducing vitamin C status (60), even though they were not considered in general guidelines and the daily additional values of vitamin C

potentially required are not currently available. These factors include: 1) passive exposure to tobacco smoking and environmental pollutants, which can enhance oxidative stress; 2) geographic influence, socioeconomic and cultural status, which may have an impact on production, selection and consumption of foods typically rich in vitamin C; 3) food preparation and cooking methods, which can reduce the content of vitamin C in foods since this vitamin is water-soluble and heat-labile.

The potential variability of the metabolism of vitamin C among various ethnic groups is practically unknown and this topic should certainly be further explored. Only one study reported that lower vitamin C concentrations were significantly associated with a higher leukocyte count in African Americans but not in Caucasians, suggesting hypothetical metabolic or pharmacokinetic differences among races (61).

VITAMIN C AND IMMUNE SYSTEM REGULATION

Besides an extensive range of biochemical pathways in which vitamin C is involved, it also participates in the response of the innate and adaptive immune system (1). The intracellular content of vitamin C in immune cells depends on the plasma availability. In healthy adults the content of vitamin C in leukocytes can be saturated with an intake of at least 100 mg of vitamin C per day, through foods, obtaining a concentration of about 3.5, 3, and 1.5 mmol/L, respectively, in lymphocytes, monocytes and neutrophils (39, 62–65). Leukocytes' absorption of vitamin C from the blood is very efficient, through SVCT proteins (66), resulting in an intracellular content which is 50 to 100 times greater than the plasma concentration (67, 68). As an effective antioxidant, vitamin C contributes to protecting neutrophils from oxidative stress during the early stages of an immune response, when neutrophils activate phagocytosis and produce reactive oxygen species (ROS) to destroy antigens (69, 70). Once the phagocytic capacity is exhausted and neutrophils start to die, vitamin C seems to regulate the process in favor of apoptosis, through the activation of a caspase-dependent cascade, inhibiting the transition to necrosis, and resulting in a more efficient resolution of inflammation (71).

Vitamin C is also involved in the migration of phagocytes (neutrophils and macrophages) toward the infection sites in response to chemoattractants (72, 73). This is particularly important since an impaired neutrophilic chemotaxis has been observed in patients with severe infection (74–76). Furthermore in subjects with low blood concentrations of vitamin C (<50 $\mu\text{mol/L}$), a daily intake of 250 mg of vitamin C can result in a 20% increase of neutrophils' migration capacity (6). Conversely, in individuals with a physiological blood concentration of vitamin C, neutrophils' mobility cannot be enhanced, as demonstrated by Bozonet et al. (4), in which neutrophils isolated from healthy volunteers and incubated with a vitamin C solution (200 $\mu\text{mol/L}$) to artificially increase their content of ascorbate did not show a major chemotactic ability.

Similarly to neutrophils, vitamin C protects lymphocytes from oxidative damage (77) and has a pivotal role in the development and function of these cells, even though the exact mechanisms have not yet been clarified (3). In T lymphocytes, vitamin C stimulates differentiation and proliferation from precursors to mature T cells, in a dose-dependent way (78). Studies on the influence of vitamin C on subtypes of T cells are mainly related to the Th1/Th2 balance. Reports underline that vitamin C can induce a shift of immune responses from Th2 to Th1 (3), while only one study suggests that vitamin C can induce the Th17 polarization of naïve CD4+ cells in murine model, affecting epigenetic mechanism (79). At present, no studies exploring the effects of vitamin C on cytotoxic T cells are available (3). In B lymphocytes, vitamin C seems to affect the production of antibodies, despite conflicting evidence (80–87). Physiological levels of Vitamin C are also necessary for normal natural killer (NK) cell development and function (3). In vitamin C-deficient mice, NK cytotoxic activity (NKCA) was lower than that in mice with normal levels of vitamin C (88), while supraphysiological levels of ascorbate do not further increase NKCA (89).

Vitamin C also regulates inflammatory response. In animal studies, vitamin C deficiency has been linked with higher circulating histamine levels, which can be rebalanced once vitamin C blood level has been normalized (90–92). Furthermore, vitamin C can reduce the production of pro-inflammatory leukocyte-derived cytokines (e.g., TNF α and IL-6), through the modulation of nuclear transcription factor kappa B (NFkB) (2, 93, 94) in at least two ways: 1) through its reduced form (ascorbate), by scavenging cellular ROS and inhibiting ROS-related signaling for the transcription of NFkB (95–98); 2) through its oxidized form (dehydroascorbate), produced as a consequence of quenching ROS, by directly inhibiting the activity of several kinases involved in the TNF α -mediated activation of NFkB (p38 mitogen-activated protein kinase, I κ B kinase α and β) (99–101).

However, the effect of vitamin C on the balance of cytokine responses (pro- and anti-inflammatory) is very complex and seems to be dependent on cell type and/or inflammatory condition (1). Moreover, authors (102, 103) have recently suggested that vitamin C may interact with molecular pathways related to inflammatory stress and immune dysfunction during sepsis, involving particular mediators: Epidermal Growth Factor Receptor (EGFR), Mitogen-Activated Protein Kinase-1 (MAPK1), Proto-Oncogene c (JUN), C-C chemokine Receptor type 5 (CCR5), Mitogen Activated Protein Kinase 3 (MAPK3), Angiotensin II Receptor type 2 (AGTR2), and Signal Transducer and Activator of Transcription-3 (STAT3).

The effects of vitamin C on immune function may also be expressed through epigenetic regulations, although this topic is still poorly understood (104, 105). The epigenetic remodeling associated with immune cell activation and differentiation includes DNA and histone modification (106). Vitamin C plays an important role by increasing the activity of epigenetic enzymes, including ten-eleven translocation (TET) proteins and Jumonij-C domain-containing histone demethylases (JHDMs)

(107). In fact, since TET and JHDMs belong to the Fe²⁺/ α -ketoglutarate-dependent dioxygenases superfamily (105), vitamin C, as ascorbate, being able to donate electrons, acts as a cofactor for these enzymes, reducing Fe³⁺ to its catalytically active form (Fe²⁺) (63). TET proteins are involved in the demethylation of cytosine residues in DNA, while JHDMs regulate the methylation of lysine and arginine residues in histones, resulting in modifications of gene transcription (63, 108, 109) that are involved in the response of both the innate and the adaptive immune system (106, 110). The utility of these recently-discovered gene-regulatory functions of vitamin C for the assessment of dietary recommendations has not yet been elucidated and further research is needed to indicate the minimum dose at which vitamin C may have an effective impact on functional or clinical outcomes through epigenetic changes (44).

ORAL SUPPLEMENTATION OF VITAMIN C FOR THE PREVENTION AND TREATMENT OF THE COMMON COLD AND UPPER RESPIRATORY TRACT INFECTIONS

The common cold is one of the most widespread viral upper respiratory tract infections (URTI), characterized by coughing, tiredness, fever, sore throat, and muscle pain, which persist for a period ranging from a few days to not more than 3 weeks (111, 112). The term “common cold” refers to an unspecific syndrome caused by several viruses, although the rhinovirus is the most frequent pathogen involved, being found in 30% to 50% of sufferers (113). Despite symptomatology usually being very mild, the common cold is a major cause of absenteeism from work and school (114). The popular myth that a very high intake of vitamin C may lead to a lower susceptibility to respiratory tract infections originates from Linus Pauling’s theories published in the seventies. According to Pauling, a daily vitamin C intake of 1,000 mg can reduce the incidence of colds by about 45% and the optimal daily intake of vitamin C to live healthily and prevent disease should be at least 2.3 g (115, 116). The response of the US market to this pioneering point of view was immediate and the sales of vitamin C dietary supplements almost doubled over a couple of years (117). However, other clinical studies with similar aims failed to demonstrate its efficacy (118–121) and, in general, contemporary authors completely refuted Pauling’s ideas, mainly based on non-randomized controlled trials or incorrect application of animal background to humans (122, 123). Although a high daily dose of vitamin C does not seem to prevent viral infections in the general population, some categories of subjects with potentially higher risk of viral infection may require particular consideration. These subjects include individuals undergoing a daily heavy physical workload such as soldiers and athletes, who may develop an immune stress condition.

General Population

If we exclude some results that reported only small or inconsistent effects attributable to vitamin C (124), after decades of investigations, the scientific community established that a high intake of vitamin C is useless in preventing the common cold (7–11), and therefore, a regular daily supplementation is not justified in the general population (12). Recent meta-analysis has reached similar conclusions regarding the incidence of infection, underlining, however, the possibility of reducing the duration of a cold. Gómez et al. (125), demonstrated that 8,472 subjects from eight randomized clinical trials (RCTs), showed very strong evidence that vitamin C intake above 80 mg/day does not prevent the common cold in healthy adults and children. Vorilhon et al. (126), analyzed eight RCTs and confirmed that vitamin C supplementation (dosage from 0.5 g to 2 g/day) is not effective, compared to placebo, in reducing the incidence of upper respiratory tract infections (URTI) in 3,135 children (from 3 months to 18 years of age), although the administration can reduce the duration of URTI by 14%, as previously highlighted by Rondanelli et al. (127). Positive results on the duration of colds was also suggested by the meta-analysis of Ran et al. (128) in which the combination of a small, long-term daily dose of vitamin C (no more than 1 g/day) to sustain immunity and a larger dose of vitamin C during the onset of the common cold (usually 3–4 g/day) was associated with the ability to relieve chest pain, fever, and chills, reducing the staying indoors duration, as well as the mean duration of disease.

People Under Heavy Physical Stress

Some authors have reported a high incidence of respiratory infections in military training centers, probably also due to an overcrowding of individuals often coming from different geographical areas (129–131). More data are available on athletes, for whom daily high-intensity training and competitions have been associated with transient immune perturbations, inflammation conditions, and increased susceptibility to infections (132–134). Furthermore, compared to the general population, athletes have a higher exposure to pathogens, due to frequent travel and sports events (135, 136), which may potentially increase the risk of developing viral infections.

Data in literature referring to the effect of vitamin C supplementation on the prevention of the common cold in these subjects are interesting, despite being limited at present. As was well described by Hemilä and Chalker, (12) vitamin C supplementation may decrease the incidence of colds by about 50% in people under extreme physical stress. More recently, Kim et al. (137) carried out a large randomized, double-blind, placebo-controlled trial in 1,444 Korean soldiers, 695 of whom received vitamin C (6 g/day) for 30 days. They showed that the vitamin C group had a 0.80-fold lower risk of getting the common cold compared to the placebo group ($n = 749$).

The theoretical basis for the use of vitamin C in physically stressed subjects resides in the significant increase of ROS production due to intense exercise (138), with remarkable

tissue damage/inflammatory response that may have harmful consequences on preventing URTI (139), possibly requiring a higher antioxidant intake compared to the general population (140). Despite this, it has recently been established that the administration of a high dose of antioxidants can negatively interfere with exercise-induced redox signaling and muscle adaptations (141–147) and the use of high doses of vitamin C to abolish ROS, especially over a long period, should be avoided (148, 149).

Even though the effects of isolated vitamin C on oxidative stress, inflammatory markers, muscle damage and immune response following exercise remain to be clarified in depth (146), a recent scientific society position stand (150), a recent review (140), and a meta-analysis (146) agree on recommending vitamin C supplementation (0.25–1.0 g/day) as an option to prevent URTI symptoms in athletes under heavy exertion and/or during periods of increased risk of infection (e.g., travel abroad) (140); athletes with low initial blood concentrations of vitamin C are the major candidates for supplementation (146, 149, 151, 152).

ORAL SUPPLEMENTATION OF VITAMIN C FOR THE PREVENTION AND TREATMENT OF PNEUMONIA

Pneumonia is a lower respiratory tract infection characterized by a cough, difficulty in breathing, chest pain, fever, and lung inflammation (153). Pneumonia is the first cause of death by infection in the United States and the fifth most common cause of death overall (154, 155). *Streptococcus pneumoniae* and *Haemophilus influenzae* are recognized as the most common agents responsible for pneumonia (156) but other pathogens are also able to induce pneumonia, including viruses and fungi (153, 154).

Results obtained in rats and mice suggested that orally supplemented vitamin C may be useful in reducing susceptibility to viral pneumonia and potentially in reducing the development of ARDS (157, 158), which is recognized as the most severe form of acute respiratory infection (159). However, human findings on vitamin C supplementation and pneumonia remain scarce, with few dated observations mainly based on particular subjects and conditions (e.g., military people, developing countries) and not generalizable (5, 160). On this topic, the most recent meta-analysis including 2,774 participants from seven clinical studies, underlined that current evidence is insufficient to sustain the efficacy of vitamin C supplementation in preventing or treating pneumonia, due to the small number of trials and very low quality of the existing results (161). However, the meta-analysis of Padhani et al. (161) considered studies from different populations, including three studies on children, without subgroup analysis. Since the pharmacokinetics of vitamin C varies between subgroups and is not yet known in children, an analysis of data should have been done independently and, therefore, conclusions of this study may be questionable.

ORAL SUPPLEMENTATION OF VITAMIN C FOR THE PREVENTION OF COVID-19

COVID-19 is a new, worldwide recognized form of viral pneumonia, caused by SARS-CoV2 infection (162, 163). The symptomatology often begins within 2 weeks from contagion and mainly includes fever, fatigue, cough, and shortness of breath (164). Current knowledge suggests that while the majority of infected subjects (80%–90%) exhibit mild symptoms or can be asymptomatic, about 5% may develop pneumonia, ARDS and multi-organ dysfunction leading to death (165).

It is unquestionable that an optimal nutritional status effectively reduces inflammation and oxidative stress, improving the immune system regulation (166). However, no data are currently available on the regular use of high doses of oral vitamin C to reduce the risk of infection by SARS-CoV2 in a healthy general population (167–169) and further studies are needed to explore the role of vitamin C in prevention of COVID-19 (169). For heavily stressed subjects (athletes in particular), specific data are not currently reported regarding the incidence, prevalence, or natural history of disease related to COVID-19 (134), despite these subjects' potentially high risk of exposure to this virus (136, 170). Furthermore, scientific opinions have not been expressed regarding the use of oral vitamin C to prevent SARS-CoV2 infection in extreme exercisers. However, a vitamin C supplementation may be effective for improving the health status of patients considered at high risk of viral infections (171).

ORAL SUPPLEMENTATION OF VITAMIN C FOR PATIENTS WITH METABOLIC DISORDERS, CARDIOVASCULAR DISEASE, AND FRAIL ELDERLY SUBJECTS: POTENTIAL RELATIONSHIP WITH COVID-19

There are notably some factors that increase the risk of developing SARS-CoV2 infection and affect the severity of COVID-19 (172). People with pre-existing non-communicable diseases (NCDs) appear to be more susceptible to developing COVID-19 (173, 174). NCDs include obesity, diabetes mellitus, chronic lung diseases, cardiovascular diseases (CVD) and various other conditions which are characterized by systemic inflammation which impairs immune response and may exacerbate the cytokine storm related to COVID-19 (173, 174).

Obese Subjects

Some studies have shown that obesity is associated to a more severe form of COVID-19 (175, 176), even in younger patients (age < 50) (177), and a BMI > 40 kg/m² was identified as a one of the strongest risks of hospitalization due to SARS-CoV2 infection (178). These findings are worrying considering that obesity is a global phenomenon and in countries such as the U.S about 36% of population is obese (179). This association could be

linked to inflammatory mechanisms, since authors suggest that, compared to individuals with a normal weight, obese subjects have a higher plasma concentration of C-reactive Protein (CRP), an inflammatory biomarker used to predict cardiovascular disease (180). Based on this, a vitamin C supplementation in these subjects may be useful in reducing inflammation, considering data that showed how a treatment of oral vitamin C (1,000 mg/day) for two months can significantly reduce plasma CRP in healthy, overweight, non-smokers with baseline CRP \geq 1.0 mg/L (181). This finding is very interesting, taking into account that participants had an adequate dietary intake of vitamin C, with a baseline mean plasma level of 57.8 μ mol/L, and it suggests that the RDAs for vitamin C in obese individuals may be underestimated, as was recently underlined by Rychter et al. (182, 183). Research is needed to understand whether by reducing the CRP with vitamin C it could be possible to influence the incidence and/or the progression of inflammation-mediated diseases associated with obesity, including infections and potentially COVID-19 (171).

Diabetic Subjects

A recent meta-analysis including 33 studies (16,003 patients) confirmed that diabetics have a two-fold higher increase in mortality, as well as severity of COVID-19, compared to non-diabetic COVID-19 patients (184). Type 2 diabetes mellitus (T2DM) is the most common form of diabetes (185), characterized by chronic hyperglycemia, inflammation and oxidative stress (186). The inflammatory condition observable in diabetes may possibly be a mechanism that increases the susceptibility to COVID-19. Low plasma concentrations of vitamin C in people with T2DM was observed (187, 188), despite adequate vitamin C intake (189, 190). Two mechanisms could particularly explain lower vitamin C levels in these patients: 1) increased urinary excretion, especially in those with microalbuminuria (191); 2) higher depletion of vitamin C caused by an increase of oxidative stress (190, 192). An interesting study on the use of oral vitamin C in diabetic subjects was reported by Mason et al. (193). It showed an approximately two-fold enhanced SVCT2 expression in skeletal muscle after vitamin C supplementation (1,000 mg for 4 months) in people with T2DM, with an increase of muscle concentration of vitamin C and a decrease of muscle oxidative stress. However, given the small number of subjects investigated in this study (seven participants, six males and one female), larger studies are needed to confirm similar results. Findings from an RCT showed that vitamin C supplementation (1,000 mg/day for 8 weeks) significantly reduced CRP, IL-6, fasting blood glucose (FBG), and triglycerides (TG) in 64 obese, hypertensive and/or diabetic patients, with high levels of CRP \geq 6 mg/L (194). In addition, meta-analytic data indicated that vitamin C supplementation for more than 30 days with a dosage ranging from 200 to 1,000 mg significantly reduces FBG in patients with T2DM (195). Based on the above, vitamin C supplementation may represent a promising option to modulate inflammation and blood glucose in patients with hyperglycemia and elevated CRP, it could potentially be able to improve the health of these individuals and reduce the susceptibility to infections. Investigations are

strongly encouraged to establish a possible correlation between an extra intake of vitamin C and a possible decrease of incidence, severity and mortality for COVID-19.

Subjects With CVDs

CVDs (as well as hypertension) are the most common comorbidities among COVID-19 patients (174, 196, 197). Individuals with a CVD are five-fold more at risk of developing the critical stage of the disease, as indicated in a meta-analysis involving over 3,000 patients with COVID-19 (198). In this case, the main reason for a higher risk of SARS-Cov2 infection is related to the high angiotensin-converting enzyme 2 (ACE2) expression observed in these patients (199–201), since this enzyme is used by the virus to invade cells, promoting viral colonization (202). It is known that low plasma concentrations of vitamin C are predictive of heightened CVD risk (203–205), but the current literature provides little support for a widespread use of vitamin C supplements to reduce CVD risk or mortality (206), and available data are also controversial. Many cohort studies and RCTs have shown no relationship between vitamin C intake and CVD risk. However, in most RCTs the participants were not prescreened for a depleted status and this seriously limits the possibility of concluding on the results, as the potential impact of the vitamin C supplementation on the outcomes considered may vary from highly significant to negligible in relation to their vitamin C status at study start (207).

A few other studies have suggested moderate benefits, and some references have registered a slight increase in risk (206). A significant barrier to the comprehension of the relationship between vitamin C and CVDs is the lack of mechanistic studies in humans (206). At present, there are no recommendations for an additional daily dose of vitamin C in CVDs to potentially prevent diseases, including pulmonary infections and COVID-19.

Frail Elderly Subjects

It is particularly important to consider elderly communities when trying to prevent COVID-19. The elderly are more vulnerable compared to the general population due to an increased risk of malnourishment and infections and a high prevalence of NCDs (208). Age itself is a risk factor for developing COVID-19 (209), due to a functional decline of the immune system (210, 211). Furthermore, malnourishment in these subjects is very frequent for several reasons (e.g., poor socioeconomic conditions, mental status, social status) (212) and nutritional deficiencies (including vitamin C) have been reported (213). Malnourishment can worsen an impaired immune system in the elderly, making them more susceptible to infections (214). In elderly hospitalized subjects (mean age 81 years) suffering from acute bronchitis or pneumonia, a mean plasma vitamin C level at baseline of 23 $\mu\text{mol/L}$ was reported and a concentration of 11 $\mu\text{mol/L}$ was found in one third of the patients (215). This is particularly important since a low vitamin C concentration (<17 $\mu\text{mol/L}$) in older people (aged 75–82 years) is considered a strong predictor of all-cause mortality (216). Notably, in Hunt's study (215) administration of vitamin C (0.2 g/day) reduced the respiratory symptom score in the more severe patients. However, at present, it is not known whether a regular

supplementation with vitamin C can protect these subjects from chronic inflammation NCDs-related and/or can prevent the onset of viral infections including COVID-19.

ORAL SUPPLEMENTATION AND SIDE EFFECTS

Vitamin C has an excellent safety profile, primarily due to its high water solubility and rapid clearance of excess levels by the kidneys (44, 217). Although it is not possible to establish a UL for vitamin C, values of 1,000–2,000 mg/day have been suggested as prudent limits by some countries, based on a potential risk of osmotic diarrhea and related gastrointestinal distress in some individuals at higher doses (44, 53).

Since vitamin C is partially converted to oxalate and excreted in the urine, high doses of vitamin C could be associated with calcium oxalate stone formation (218, 219). Ferraro et al. (220) studied 156,735 women and 40,536 men, who reported episodes of kidney stones during an average follow-up of 11.3–11.7 years. The authors significantly correlated the total vitamin C intake with a higher risk of incident kidney stones in men, but not in women. However, it is important to outline that this study had limitations to be considered. The presence of confounding factors (e.g., comorbidities, dehydration, dietary intakes of oxalate-forming foods) were not taken into account during the follow-up, and the authors assessed vitamin C intake only through a questionnaire (without measuring blood levels) and with very long time intervals (every 4 years).

INTRAVENOUS ADMINISTRATION OF VITAMIN C: A POTENTIAL ROLE IN THE TREATMENT OF COVID-19?

While an extra dietary intake of vitamin C to counter pneumonia does not seem promising, several interesting data have emerged from the use of vitamin C through IA, providing an encouraging, but questioned, hypothesis on its potential pharmacological use for the treatment of pneumonia caused by SARS-CoV2 infection. In fact, as opposed to oral supplementation, in which the maximum peak plasma concentration that was achieved with a high-dose (3 g every 4 h) was 220 $\mu\text{mol/L}$ (221), the IA of vitamin C, bypassing the limitations induced by intestinal transporters (SVCT1), may lead to a higher plasma level (e.g., up to 3,000 $\mu\text{mol/L}$ at day 4 with 200 mg/kg/day, administered in 50 mg/kg/dose every 6 h).

Although the potential antiseptic therapeutic mechanism exerted by vitamin C has not yet been understood (103), besides the effects described in the previous paragraphs, the use of vitamin C in an infectious emergency may be justified for some reasons: 1) significant clinical evidence from pneumonia, critical illnesses and other acute infections suggests that plasma levels of vitamin C can rapidly drop off (e.g., <30 $\mu\text{mol/L}$) during the inflammatory response (2, 93, 94, 222–228) probably due to an increased

consumption of vitamin C by leukocytes. Considering that intracellular ascorbate concentrations in mononuclear cells and in granulocytes are respectively 80 and 25 times greater than in plasma, an increased replacement and turnover of these cells during these medical conditions can contribute to a decrease of vitamin C in the blood (229); 2) a negative regulation of SVCT2 transporters induced by inflammatory cytokines, in particular IL-1 β and TNF α (230); 3) the antioxidant defense system of the pulmonary epithelium involves enzymes and vitamin C (231) and according to Banerjee and Kaul, a sustained high dose of vitamin C available in respiratory secretion could exhibit an effective anti-viral activity (232). This last point, however, is still a hypothesis at present, since the level of vitamin C in the bronchoalveolar fluid is normally too low to achieve anti-viral activity and furthermore very little is known about the potential increase of vitamin C concentration in bronchial tissue and fluid secretion following a high-dose IA (36).

Therefore, considering the aspects mentioned above, the infusion of vitamin C has recently been suggested to treat COVID-19 in ICU hospitalized patients (13–18). Below, we summarize the most substantial evidence obtained in critical illness studies based on IA of vitamin C regarding the most relevant outcomes (inflammation, ventilation time, and mortality) which may relate to SARS-CoV2-induced ARDS.

Effects of IA of Vitamin C on Inflammation Markers

In COVID-19 patients the inflammatory response is very dramatic and has been defined as a “cytokine storm”, associated with increased plasma concentration of IL-1 β , IL-2, IL-6, IL-10, IFN γ , and TNF- α (233, 234), able to induce an acute lung injury (ALI) which results in ARDS and requires urgent ICU interventions (162). Physiopathology of ARDS involves alteration of pulmonary permeability, rapid lung leukocyte infiltration with a large increase

of tissue oxidative stress, leading to respiratory failure and death, which in most cases is due to massive alveolar damage (24, 235). A promising background on the use of vitamin C in an experimental model of ALI was found (236–241), with positive evidence on rebalancing cytokine production and specific physiopathological mechanisms involving neutrophils (i.e., neutrophil extracellular traps) (4) which may contribute to organ damage and mortality in COVID-19 (233) (**Figure 1**). Two studies by Fowler et al. are currently available on IA of vitamin C in ICU hospitalized patients and inflammatory response, with mixed results (227, 242). In the first preliminary study (227), vitamin C showed a significant reduction in proinflammatory biomarkers (CRP and procalcitonin) over the first 96 h, without adverse effects registered during the infusion, but the number of ARDS-affected patients treated with vitamin C was too small (50 mg/kg/24 h, n = 8; 200 mg/kg/24 h, n = 8) to allow safe conclusions. In the second larger study (242), 167 patients with sepsis and ARDS were randomized to receive vitamin C (50 mg/kg every 6 h for 96 h) or placebo; no changes in CRP and thrombomodulin were detected, although the study was criticized for the choice of the inflammatory markers assessed (243).

Effects of IA of Vitamin C on Intensive Care Ventilation Time

The above-mentioned study (242) also reported a lower duration time of mechanical ventilation support in the supplemented group, with a higher number of ventilator-free days in the vitamin C group than in the placebo group (mean values: 10.6 vs. 13.1 days, respectively). Ventilator-free days were defined as the number of extubated days, considering the time between ICU hospitalization and day 28. Another previous randomized controlled trial (RCT), including burn patients with severe respiratory dysfunction receiving a very high dose of vitamin C

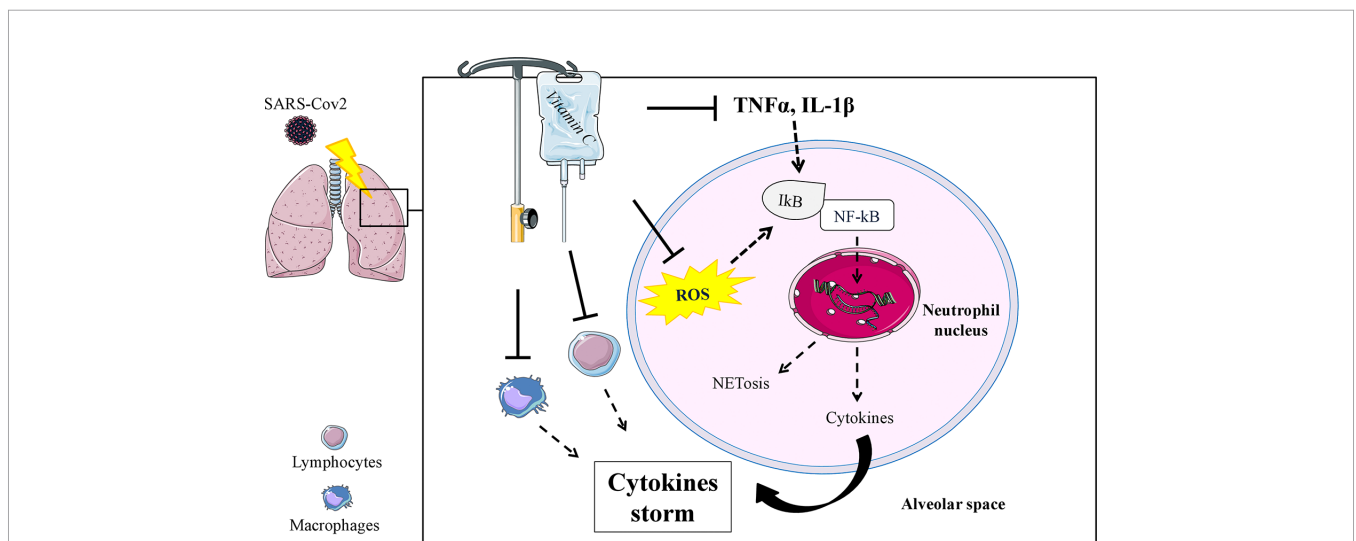


FIGURE 1 | Schematic mechanism in which an IA of vitamin C could modulate specific functions of neutrophils (ROS and TNF α , IL-1 β mediated), inhibiting pathways involved in the Neutrophil Extracellular Trap formation (NETosis) and reducing the uncontrollable inflammatory cytokine production in the alveolar space. Potential effects on reducing cytokine production have also been speculated in lymphocytes and macrophages. ROS, reactive oxygen species; NFkB, nuclear transcription factor kappa B; \perp , inhibition stimulus; dashed arrow, reduced effect or production.

(66 mg/kg/h for 24 h), showed a significant decrease of the time of ventilation (mean values: 12.1 vs. 21.3 days, respectively) in those who received vitamin C infusion compared to the control group (85). The pulmonary benefit reported by these authors is probably due to the antioxidant, anti-inflammatory and microvascular action of the vitamin C (244).

Different positions on the topic derive from systematic evaluation of the literature, suffering because of the gross limitations of the available primary data. For example, the meta-analysis of Langlois et al. (245), failed to find any improvement on ventilation time. This work, however, included studies with vitamin C administrated through different routes (enteral or parenteral), most of which (9 out of a total of 11 studies) used antioxidant mixtures instead of vitamin C alone; Zhang and Jatava (244) analyzed the efficacy of IA of vitamin C on vasopressor sparing effects and the lower need for mechanical ventilation in critical illness, underlining several weaknesses of the available studies considered (four RCTs and one retrospective review), such as the paucity of the sample size, the heterogeneity of subjects enrolled, hospitalization setting, dosages and follow-up; recently, the meta-analysis from Hemilä and Chalker (246), including eight trials and 685 patients, with promising results on ventilation time, pointed out that the great variation in the reported effects of vitamin C may be linked to the non-homogeneous severity of the illness which mostly impacts the ventilation time required. From this point of view, vitamin C shortened ventilation time on average by 25% when the analysis was restricted to patients requiring mechanical support for more than 10 h.

Effects of IA of Vitamin C on Mortality





Of the critical outcomes considered the potential effect of vitamin C on mortality rates appears to be the most controversial one, with RCTs studies that underline promising results which are not supported by recent meta-analysis. A significant reduction of 28-day mortality during ICU hospitalization was observed in a small group of patients with sepsis treated with IA of vitamin C

(25 mg/kg every 6 h, for 72 h) compared to the control group (14.28% Vs. 64.28%, respectively) (247). More recently, findings from the CITRIS-ALI study (242) showed a reduced mortality at day 28 in the vitamin C group (29.8%) compared to the placebo group (46.3%). Conversely, according to the meta-analysis of Zhang and Jatava, although vitamin C IA seems to be linked to positive vasopressor effects, temporally reducing the need for mechanical ventilation, no positive effect in favor of overall mortality emerged (244), leading the authors to conclude that it does seem improbable that vitamin C, considered as a single agent, could be so dramatically decisive on the physiopathology of a critical illness as to influence the incidence of mortality (244). Similar conclusions were drawn by Wei et al. (248), who, by including recently published retrospective studies in their meta-analysis, suggest the lack of benefit on 28-day mortality, both in ICU and in-hospital patients with sepsis.

It is important to consider that the effect of vitamin C infusion seems to exert different results on mortality in relation to the type of critical patients involved, especially when administration is in association with other drugs. From this point of view, two retrospective studies showed that vitamin C (1.5 g every 6 h), in combination with hydrocortisone (50 mg every 6 h), and thiamine (200 mg every 12 h) may dramatically reduce mortality by 56% in ICU patients with severe pneumonia (249) and by 79% in severe sepsis (250), compared with patients who did not receive vitamin C and thiamine. Unlike these data, a recently published RCT (VITAMINS) showed no benefit from the combination of IA of vitamin C, hydrocortisone and thiamine in comparison to hydrocortisone alone among patients with septic shock (251). However, as underlined by Carr (252), since the VITAMINS trial did not include a monotherapy vitamin C subgroup, this trial does not provide any information as to whether IA of vitamin C offers some benefit to septic patients in the absence of corticosteroid administration, and further trials are needed in this direction.

Another critical issue that should be highlighted is the timing of treatment administration. On this topic, important results

TABLE 1 | Summary of research findings on the use of vitamin C in humans.

General population		There are no recommendations that vitamin C supplementation impacts the incidence and duration of the common cold or pneumonia, and regular supplementation is not currently justified in the general population. Data on pneumonia are less clear in children, because the pharmacokinetics of vitamin C in this category is unknown at present. A supplementation of 0.2 g/day of vitamin C may be reasonable in subjects with low plasma vitamin C concentration.
Subjects with NCDs		Subjects with noncommunicable diseases (NCDs) and frail, elderly subjects are recognized as being at high risk of viral infections. Vitamin C supplementation (0.2–1 g/day) can reduce inflammation and, although direct evidence is still lacking, it may decrease the susceptibility to infections and/or the severity of the disease. Vitamin C supplementation (0.2 g/day) may reduce the respiratory symptoms in elderly patients.
Heavy stressed subjects		Vitamin C supplementation may decrease the incidence of colds in people under extreme physical stress. Vitamin C supplementation does not seem to improve physical performance in well-nourished athletes, and regular high-dose vitamin C supplementation may interfere with the exercise-induced redox signaling adaptation and should be avoided. Athletes should consider a vitamin C supplementation (0.25–1 g/day) to prevent URTI symptoms during limited periods of enhanced heavy stress (e.g., sports competitions).
Hospitalized patients		In critically ill patients, vitamin C deficiency is common, and IA of high doses has been used to normalize plasma vitamin C levels. To date, no recommendations are available as few data on inflammatory markers, mechanical ventilation time and mortality rates have been reported in these patients. Further controlled studies are encouraged, especially for COVID-19.

come from a retrospective cohort study of 208 patients in septic shock (253), which suggested that the ICU mortality ratio [based on the APACHE (Acute Physiology and Chronic Health Evaluation)-predicted ICU mortality] of patients who received vitamin C with thiamine and hydrocortisone, increased linearly with the delay in treatment from initial sepsis presentation. Indeed, the APACHE-adjusted ICU mortality was significantly reduced only in patients who received vitamin C, thiamine, and steroids within 6 h from sepsis presentation (253).

CONCLUSION

Apart from some specific individuals and conditions (Table 1), the evidence described is insufficient to support the efficacy of a regular supplementation with vitamin C for the prevention or treatment of the common cold or pneumonia in the general population. Interesting data on the possible use of vitamin C to prevent infections regard special conditions (e.g., soldiers and athletes) and subjects with metabolic disorders, CVDs or frailty, in which the potential control of inflammation by a vitamin C supplementation could represent an effective aid in reducing the risk of infection, even for COVID-19. However, this last statement needs to be properly supported by future RCTs. Even though the IA of vitamin C could be an adjuvant therapy to quickly restore plasma levels of vitamin C during severe sepsis and ARDS in ICU hospitalized patients (254), its effects on inflammation response, ventilation time and mortality rates still

remain uncertain and results from further RCTs, especially in COVID-19 patients, are urgently needed.

Although a significant increase in vitamin C sales was registered immediately after the global pandemic state of emergency was declared, at present, there is no evidence that vitamin C supplementation can protect people from the SARS-CoV2 infection (255). At the current state of knowledge, health care professionals have the responsibility to guarantee that patients have correct information regarding the lack of data supporting the efficacy of this supplement for the prevention and/or treatment of COVID-19 (167, 168).

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version. GC and MN conceived the original idea of the manuscript and contributed equally to this work as main authors. GD'A revised the manuscript before submission.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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