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Identifying Predictive Biomarkers of Oxidative Stress in COVID-19: The Role of Vitamin D, Calcium, and Vitamin E

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Abstract

COVID-19 is a viral infection caused by the SARS-CoV-2 virus, amplifying global health complexities. An important part of the knowledge of the disease and ways to prevent it is the search for biomarkers for the assessment of the occurrence of oxidative stress in patients with COVID-19. Thus, the current review is concerned with the functionality of Vitamin D, Calcium, and Vitamin E as biomarkers to predict the level of oxidant strain in COVID patients. Vitamin D is proven to possess immunomodulatory and antioxidant functions, regulatory effects on the antioxidant enzyme, and cytokine inhibitory effects. Analyzing clinical trials suggests the association of low Vitamin D levels with higher coronavirus threat, hence the possibility of the vitamin as a biomarker of coronavirus advancement. Calcium is a biologically active ion that participates in many processes within a cell and contributes to oxidative stress regulation; in COVID-19 patients, their calcium balance becomes disrupted, with hypocalcemia being particularly ominous. Lastly, Vitamin E, which is a lipid-soluble, antioxidants strengthens cell membranes by eliminating free radicals and further regulates the immune system. Initial case-control research findings suggest that sufficient Vitamin E can enhance the clinical outcomes of COVID-19 patients because of the decrease in oxidative stress. This review concerns the current state of knowledge about these micronutrients, including their biochemistry and clinical data, and their potential applications in the treatment of COVID-19.

Keywords: COVID-19, oxidative stress, Vitamin D, Calcium, Vitamin E

Introduction

The novel SARS-CoV-2 virus or COVID-19 has had a significant impact on health and the global economy since it was first discovered in late 2019 (Acter et al., 2020). The rapid infectivity of the virus, its associated severe respiratory illness, and its potential for multi-organ injury have prompted increased focus on understanding the pathophysiological mechanisms of the disease and devising treatments and management approaches (Lopes-Pacheco et al., 2021). Biological stress (oxidative) is a very critical factor in COVID-19 infection, which is very much related to the progress and severity of the condition (Beltrán-García et al., 2020). The knowledge of biomarkers of oxidative stress in COVID-19 patients for diagnosing the disease at an early stage, estimating the prognosis, and selecting an effective treatment strategy is crucial. Biological stress (oxidative) involves an increase in the levels of ROS and the inability of the body to remove the reactive intermediates or a deranged repair mechanism of the resulting damage (Del Valle et

al., 2015). ROS are cytotoxic agents that can produce DNA damage, protein oxidation, and lipid peroxidation which cause cell death and tissue injury at very high concentrations (Barrera, 2012). About COVID-19, oxidant stress is associated with a hyperinflammatory state or cytokine storm which causes ARDS and multi-organ dysfunction. Hence, determining oxidative stress biomarkers that could help in identifying the extent of oxidative stress in COVID-19 can help researchers unravel the disease's mechanism and recommend precise therapeutic approaches (Georgieva et al., 2023).

Out of all micronutrients, Vit-D, Calcium, and Vit-E have received much attention when it comes to the regulation of biological stress (oxidative) and immune responses (Elmadfa & Meyer, 2019). Micronutrients are critical for cellular metabolism and have shown value as biomarkers and treatment targets in numerous diseases, including viral illnesses (Pecora et al., 2020). The purpose of this review is to briefly discuss how Vit-D, Calcium, and Vit-E will function in oxidative stress for COVID-19 patients can be used as biomarkers. Vitamin D is a fat-soluble vitamin, which is extremely important for the body in terms of calcification, bones, and teeth, and has an important immune function. Apart from the classical functions, Vitamin D has been established to possess antioxidant activity (Aranow, 2011). It also increases the concentration of antioxidant enzymes like SOD and GPx and decreases the levels of pro-inflammatory cytokines including TNF-α and IL-6 (Sedaghat et al., 2021). These properties indicate that Vitamin D may assist in reducing inflammation and biological stress (oxidative) in COVID-19. Studies on the epidemiology of COVID-19 have shown that patients with low Vitamin D levels are more vulnerable to getting infected and having severe disease (Ye et al., 2020). Therefore, there is a possibility that identifying the association of Vitamin D status with oxidative stress in COVID-19 may reveal further preventive and treatment options.

Calcium is an essential structural and functional component of the cells, participating in processes such as signal transduction, muscle contraction, and neurotransmitter secretion (Brini et al., 2014). It also has a massive role in ensuring that the oxidation process within cells is balanced. Calcium ion is involved in signaling pathways that control the generation and elimination of ROS (Bertero & Maack, 2018). Increased oxidative stress and inflammatory reactions may also occur from the disruption of calcium balance and promote disease progression (Podkowińska & Formanowicz, 2020). Hypocalcemia, in COVID-19 patients, has been a prevalent finding that appears to be associated with severe disease processes (Di Filippo et al., 2021). The study on the interrelation between calcium levels and oxidative stress indicators, as well as determining their potential as outcome predictors in COVID-19, could contribute to patient risk stratification and treatment planning (Kotnis et al., 2022). Vit-E is an antioxidant (fat-soluble) that helps protect the cell membrane against oxidative damage by neutralizing free radicals. There are eight types in total, with alpha-tocopherol being the most effective in the body (El-Aal, 2012). In addition, Vitamin E is known to affect immune responses and reduce oxidative stress as well as improve endothelial function (Lewis et al., 2018). Thus, it can be a therapeutic agent for conditions with high oxidative stress and inflammation, including COVID-19. The first recent investigations indicate that there is a relationship between sufficient levels of Vitamin E and better results in COVID-19 outcomes (Erol et al., 2020). This review will therefore summarise existing literature concerning these micronutrients concerning their biochemical role, existing research, and potential role in COVID-19 management. This paper is intended to discuss the possibilities of these micronutrients to serve as predictive biomarkers to understand COVID-19 pathophysiology and aid in the creation of evidence-based therapeutic strategies.

Biochemical Mechanism of Vitamin D in Oxidative Stress and COVID-19

Vitamin D is used primarily as calcium and phosphate and for the maintenance of bone health but has also immunomodulatory and antioxidant effects (Sîrbe et al., 2022). Calcitriol which is the active form of vitamin D, influences its target cells by binding to the vitamin D receptor, which is present in all the nucleated cells and also in many immune cells like T cells, dendritic cells, and macrophages (Sîrbe et al., 2022). This binding begins the transcription of many genes concerned with immune response regulation and free radicals scavenging. Vitamin D upregulates the antioxidant enzymes like CAT, GPx, and SOD. These enzymes have vital functions in combating free radicals and shielding cells from biological stress (oxidative) and scarring (Srivastava et al., 2017). For example, SOD drives the conversion of superoxide radicals to hydrogen peroxide and oxygen, and catalase and GPx then convert hydrogen peroxide to water and oxygen thereby eliminating potentially damaging intermediates (Bhattacharya, 2014). Moreover, Vitamin D also can regulate inflammatory cytokines. These include interleukin-6, tumor necrosis factor-alpha, as well as other cytokines relevant to the inflammatory response (Liu et al., 2018). Vitamin D thus reduces inflammation levels, and the free radicals that result from high inflammation levels can also be countered (Liu et al., 2018). This bimodal function of increasing antioxidant protection and decreasing inflammation makes Vitamin D an important factor in protection against oxidative stress in situations involving pathologies such as COVID-19-associated inflammation (Sestili & Fimognari, 2020).

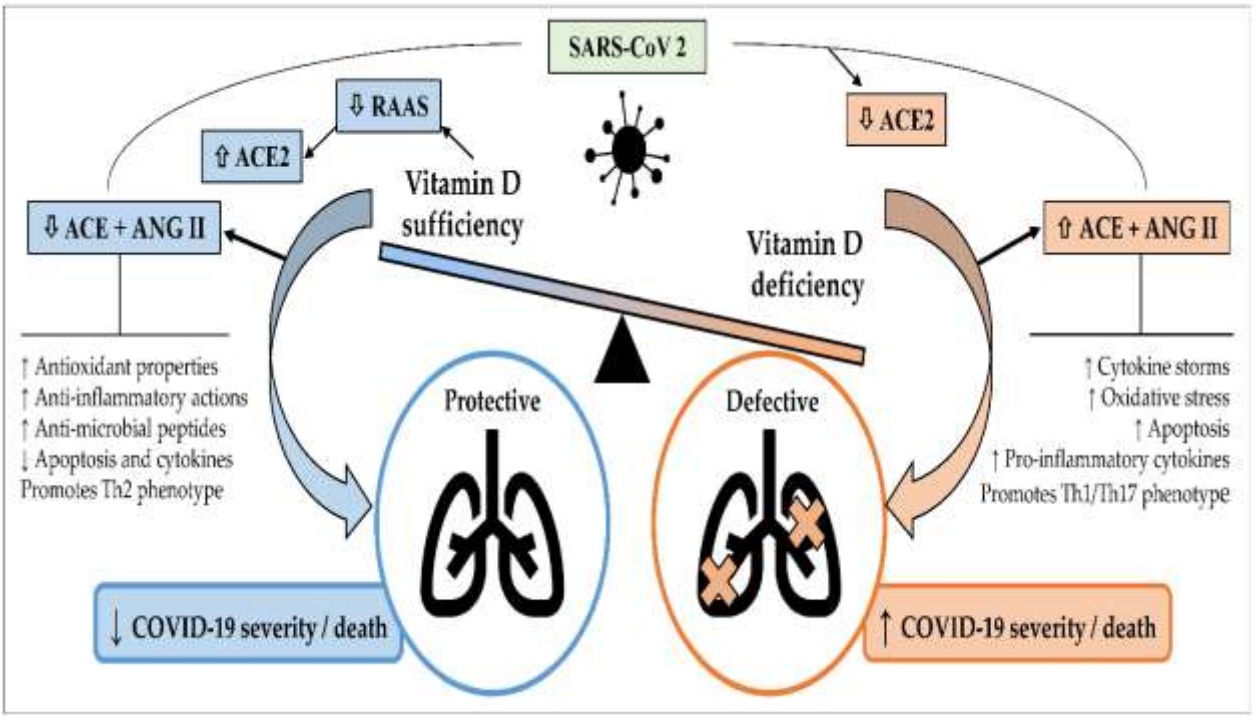

Figure 1: Mechanism of vitamin D and protective effects against COVID-19 and lung injury (Ghelani et al., 2021).

Predictive Biomarkers of Oxidative Stress in COVID-19

The involvement of oxidative stress in the development and worsening of COVID-19 is quite evident. It takes place when ROS generation surpasses the body's neutralizing ability, thus causing cellular dysfunction (Afzal et al., 2023). Such abnormality in the immune system in COVID-19 patients leads to increased levels of inflammation and destruction of tissues, which in turn contributes to the severity of the

disease (Xie et al., 2021). Many biomarkers can be considered as indicators of oxidative stress in COVID-19, such as MDA, AOPP, and TBARS (Da Silva et al., 2024). These biomarkers have been found to correlate with higher levels of disease severity, worse clinical prognosis, and higher mortality (Tjendra et al., 2020).

Higher internal oxidative stress biomarkers are associated with more severe conditions such as the ARDS, multi-organ failure, and other complications of COVID-19 as identified in the study by Robba et al. (2021). For instance, the augmentation in MDA has been associated with lung injury and reduced lung capacity, which are the characteristics of critical COVID-19 patients (Mehri et al., 2021). Furthermore, there is the probable reduction of the key antioxidant, glutathione, in COVID-19 patients which inadvertently increases oxidant stress and weakens the body's ability to neutralize dangerous ROS (Labarrere & Kassab, 2022). These biomarkers can therefore be used to assess the patient's oxidative status and probably inform on therapeutic management that targets the alleviation of oxidative stress including the use of antioxidants (Cumpstey et al., 2021). Assessing the prognostic potential of OS markers in COVID-19 will help better identify the disease in its early stages and stratify patients according to individual risk, which would enable the development of effective treatment plans. Thus, when recognizing patients who can potentially have poorer outcomes, medical practitioners can allocate precious medical resources and apply specific interventions to alleviate the effects of oxidative stress on the patient's disease status.

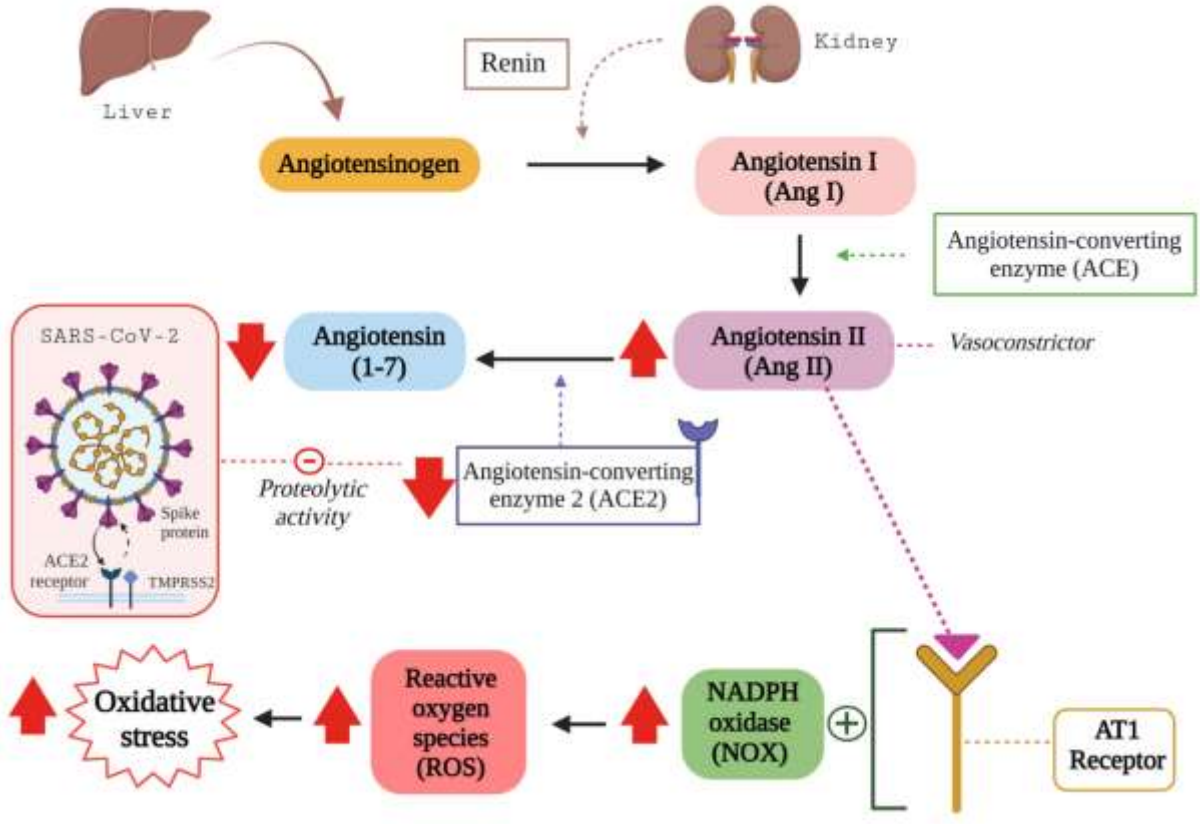

Figure 2: SARS-CoV-2 pathway of Oxidative Stress in COVID-19 (Mingoti et al., 2022).

Discussion

Consumption of Vitamin D has been under investigation, especially concerning the immunity and the possible vulnerability to COVID-19. Some observational studies suggested that having lower levels of

Vitamin D makes a person more vulnerable to severe infection, and other complications. Several researchers have established that low levels of Vitamin D increase the risk of severe forms of COVID-19, as well as the likelihood of requiring a ventilator, being admitted to the ICU or intubation, and possibly, death; conversely, sufficient Vitamin D makes patients less likely to experience severe outcomes of COVID-19 (Campi et al., 2021). A big retrospective cohort study conducted in May 2020 by Hastie and his research group also showed that low levels of Vitamin D were linked to SARS-Cov-2 positivity and mortality (Hastie et al., 2020).

However, supplementation studies appear to have some encouraging timeframe evidence. An RCT conducted in Spain demonstrated that patients on high doses of calcifediol (25-hydroxyvitamin D3) had a significant reduction in ICU admission and mortality compared to the control group (Castillo et al., 2020). Therefore, observing the efficacy of vitamin D supplementation is important in treating COVID 19 as demonstrated in this study. Similarly, Pereira et al. (2020) conducted an analysis on the role of Vitamin D in COVID-19, and the authors found fatality rates associated with Vitamin D deficiency to be higher and recommended that supplementation of Vitamin D could be a cost-effective intervention in reducing the burden of COVID-19 (Pereira et al., 2020). All these findings combined underscore the necessity of having sufficient Vitamin D levels in the body through diet, taking supplements, or moderate sunbathing as a preventable and curative method of COVID-19.

This oxidative stress and inflammation that is related with COVID-19 has been thought to be alleviated by vitamin E, which is a substance that is known to be an antioxidant. While there is less scientific evidence on Vitamin E compared to Vitamin D concerning COVID-19, several recent studies point to the positive impact of Vitamin E on disease control. A preliminary and cross-sectional study pointed out that higher levels of Vitamin E were significantly correlated with improved clinical status in COVID-19. According to the research, patients with higher plasma Vitamin E concentrations were associated with lower concentrations of inflammatory Bio Markers like C-reactive protein and Interleukin-6. This correlation indicates that Vitamin E may possess antioxidant activity that might be useful in controlling inflammation of severe COVID-19 (Saadat et al., 2020). Furthermore, Vitamin E supplementation appears to improve immune function, which is beneficial in elderly people who are in more danger of developing serious COVID-19 symptoms. For example, a clinical trial exploring the effects of Vitamin E supplementation in elderly patients indicated that T-cell function was enhanced and oxidative stress biomarkers decreased in those taking Vitamin E supplements (Wu et al., 2008).

Moreover, supplementation with a cocktail of antioxidants such as vitamin E has been mentioned as a possibility to modulate oxidant stress in COVID-19. Alagawany et al. (2021) reviewed the potential advantages of antioxidant cocktail strategies such as vitamin E" to modulate oxidative injury and inflammatory processes in COVID-19 patients (Alagawany et al., 2021). Despite these findings, further conclusive human trials were needed to strengthen the outcome in favor of Vitamin E in such circumstances. Additionally, early studies indicate that Vitamin E, combined with other therapies, can enhance patient prognosis. Thus, further extensive research is needed to confirm these observations and define definite doses of Vitamin E for COVID-19 treatment. Therefore, Vitamin E supplement owing to its antioxidant and immune regulating effects might be a helpful additional therapy for COVID-19. A dietary modification may be to increase or supplement Vitamin E which may be useful to minimize the progression of the disease and enhance patient results. However, more extensive clinical trials are required to determine standard treatment plans and appropriate dosing schedules for administering Vitamin E for COVID-19.

Conclusion

In COVID-19, inflammation is mediated through oxidative stress and causes severe inflammation and cell damage in those affected. Understanding and using prognostic biomarkers and therapeutic targets that either mitigate or enhance oxidative stress are critical in enhancing patients' prognosis. In this review, the responsibilities of Vitamin D, Calcium, and Vitamin E, including their function as diagnostic biomarkers and treatment targets for oxidative stress in COVID-19 individuals, have been discussed. As an immunomodulator with demonstrated antioxidant effects, vitamin D can prove rather effective in taming COVID-19 severity and death. Multiple clinical trials have shown a correlation between clinical outcomes in patients and proper Vitamin D levels; therefore, supplementation could be a straightforward and inexpensive means to strengthen the immune system and minimize the severity of the infection.

Significant impacts of calcium on cellular and mitochondrial function have been linked to the breakdown of calcium homeostasis, which has been related with poor outcomes in COVID-19. By monitoring and controlling calcium levels in COVID-19 patients, it may be possible to gain a better understanding of the progression of the disease and contribute to the development of treatments that are tailored to the underlying cause. Vitamin E, which is a powerful antioxidant that may neutralize free radicals, has also been shown to be effective in enhancing immunological responses and reducing oxidative stress in patients with COVID-19. Even though preliminary research has produced some encouraging results, larger and more reliable clinical trials are necessary to investigate whether or not vitamin E supplementation is effective in treating this ailment. This would be a helpful strategy to lessen the severity of COVID-19 and maybe improve the health outcomes of patients, therefore, it is possible to hypothesize that individuals should make sure they eat sufficient amounts of vitamin D and vitamin E, either through their food or through supplements. They may be effective as supporting interventions in the overall fight against COVID-19 because these nutrients are involved in controlling redox and immunological activities. To verify these facts and establish standard recommendations for their application in clinical practice, additional research and clinical studies are going to be conducted.

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