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Associations between Inflammatory Markers, Micronutrients, and Disease Severity in COVID-19 Patients with Type 2 Diabetes Mellitus

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ABSTRACT

The management of treatment strategies in COVID-19 is critical, especially in patients with type 2 diabetes. Non-enzymatic glycation of transmembrane protease serine 2 and angiotensin-converting enzyme 2 during COVID-19 in patients with diabetes may exacerbate immune dysregulation and inflammation. Elevated inflammatory cytokines such as IL-1, IL-2, IL-6, IL-7, and IL-10, tumor necrosis factor-α, interferon-γ, granulocyte-macrophage colony-stimulating factor, and monocyte chemoattractant protein-1 have been observed in COVID-19 patients. This review aims to assess the relationship between inflammatory markers, including C-reactive protein, and micronutrients (vitamins D and C, zinc, and copper) with the severity of COVID-19 infection in patients with type 2 diabetes. A narrative review was conducted through a comprehensive literature search of English-language articles published between 2000 and 2025. The databases searched included PubMed, Scopus, the ISI Web of Science, Cochrane, and Embase. Search terms included COVID-19, infections, type 2 diabetes mellitus, interleukins, and micronutrients. English-language scientific articles, systematic reviews, and meta-analyses were included, while studies lacking sufficient information, letters, comments, and editorials were excluded. Evidence suggests that immune-boosting components such as proteins, vitamins, and minerals can enhance immunity to infections. Vitamins D and C, zinc, and copper play supportive roles in immune function, potentially modulating the inflammatory response in COVID-19 patients with type 2 diabetes. High levels of inflammatory cytokines correlate with increased disease severity in this population. Understanding the interplay between inflammatory markers and micronutrients may guide improved therapeutic strategies for managing COVID-19 in diabetic patients. Further research is warranted to clarify these relationships and optimize clinical outcomes.

Keywords: Coronavirus disease; Infections; Interleukins; Micronutrients; Type 2 diabetes mellitus

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), quickly became a global health disaster.[1,2] Currently, several human evaluations of

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approved therapeutic management for other diseases in combination with nutritional supplements such as zinc and vitamin D have been conducted for COVID-19.[3,4] The state of the disease varies from an asymptomatic condition to hospitalization. Coronaviruses can damage the lungs, digestive system, liver, heart, kidneys, and nervous systems. This virus activates both innate and adaptive immune responses. In response to COVID-19 infection, a cytokine storm is induced through the excessive release of interferon-α (IFN-α), IFN-γ, interleukin-1β (IL-1β), IL-6, IL-12, tumor necrosis factor-α (TNF-α), and transforming growth factor (TGF-β), as well as chemokines such as C–C motif ligands (CCL2, CCL3, and CCL5), and C–X–C motif ligands (CXCL8, CXCL9, and CXCL10).[5] Ultimately, this event contributes to acute respiratory distress syndrome (ARDS) and may increase vascular permeability, disseminated coagulation, multiorgan failure, and death. This release first occurs in the early stages of infection by innate immune cells, but cytokine storms occur in the later stages of infection, and adaptive immunity is highlighted rather than the innate immune response.[4] SARS-CoV-2 enters human cells via angiotensin-converting enzyme 2 (ACE2); this enzyme is essential for inhibiting the renin-angiotensin system (RAS), but the viral attack reduces enzyme expression at the cell surface, resulting in vasoconstriction, inflammation, and thrombosis.[6] *ACE2* is expressed in the liver. This binding of the virus and host cell may induce insulin resistance and at least in acute infection, increases blood sugar.[7] The inflammatory response probably contributes to type 2 diabetes mellitus (T2DM) incidence by causing insulin resistance[8] (Figure 1).

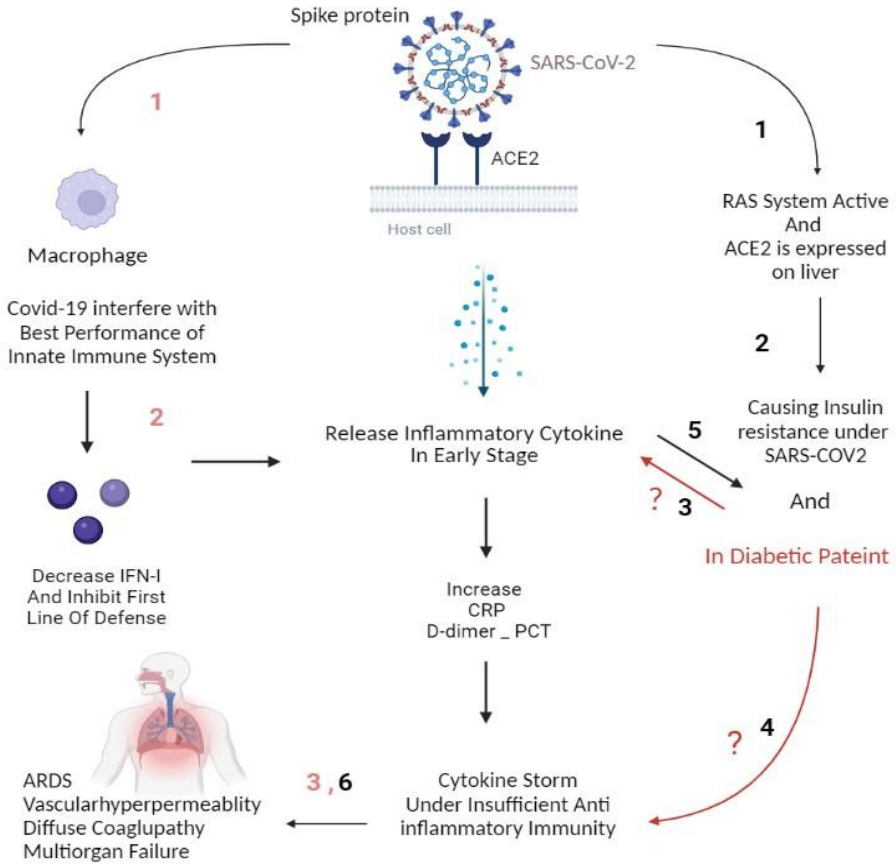


Figure 1. Proposed mechanisms linking SARS-CoV-2 infection with inflammation and insulin resistance. Binding of the viral spike protein to angiotensin-converting enzyme 2 (ACE2) may activate inflammatory signaling pathways, leading to increased production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). These cytokines can interfere with insulin signaling and contribute to insulin resistance. Inflammatory responses may further impair glucose homeostasis, potentially exacerbating metabolic dysregulation in patients with type 2 diabetes mellitus. Solid arrows indicate established pathways, whereas dashed arrows represent proposed or indirect mechanisms.

Diabetes is identified as a major risk factor for COVID-19 especially given the abundant transfer rate of this infection and the global spread of diabetes.[9] Diabetes is known as an inflammatory disease that has been reported to elevate inflammation by increasing the release of TNF-α and IL-10.[10]

patients with diabetes are at a higher risk of developing severe complications when infected with SARS-CoV-2. Studies have shown that diabetes is associated with increased rates of hospitalization, intensive care unit admission, and mortality. This elevated risk is attributed to the chronic inflammatory state and impaired immune response commonly seen in diabetic individuals, which can exacerbate COVID-19 outcomes.[11] In patients with diabetes, uncontrolled hyperglycemia can increase the expression of *ACE2* and *TMPRSS2*, along with non-enzymatic glycosylation, which can enhance the infection of COVID-19 by supporting the cellular entry of SARS-CoV-2[12] (Figure 2).

In summary, the interaction between SARS-CoV-2 infection and T2DM presents a complex challenge, as diabetes not only predisposes patients to more severe COVID-19 outcomes but also exacerbates inflammatory responses through multiple pathways, including increased cytokine release and altered *ACE2* expression. Understanding these mechanisms is critical for developing effective therapeutic strategies, particularly those involving nutritional supplements and anti-inflammatory approaches. This review aims to synthesize current evidence on the inflammatory markers and micronutrients involved in COVID-19 progression in diabetic patients, highlighting potential avenues for improving clinical management and patient outcomes. Here we highlight the key status of inflammatory markers, minerals and vitamins under the condition of COVID-19 with type 2 diabetes.

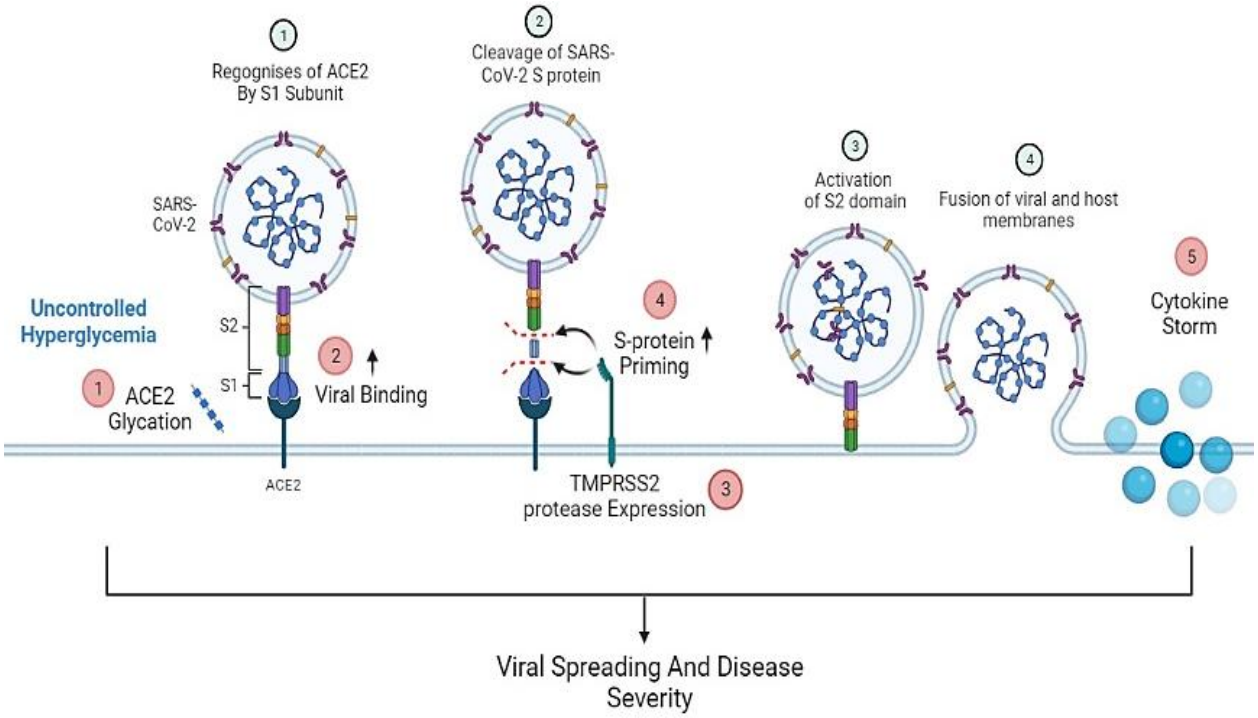


Figure 2. Potential effects of uncontrolled hyperglycemia on SARS-CoV-2 entry and host inflammatory responses. Chronic hyperglycemia may promote non-enzymatic glycation of host proteins, including ACE2 and transmembrane protease serine 2 (TMPRSS2), which has been proposed to influence viral binding and spike protein priming. Following ACE2 binding and TMPRSS2-mediated cleavage, viral entry into host cells occurs through membrane fusion or endocytosis. Hyperglycemia-associated oxidative stress and inflammatory signaling may further amplify cytokine production and endothelial dysfunction, contributing to disease severity. The depicted pathways represent proposed mechanisms based on available experimental and clinical evidence.

MATERIALS AND METHODS

A comprehensive literature search was conducted in the following databases: PubMed, Scopus, Web of Science, Cochrane, and Embase for relevant papers published between 2000 and August 2025 that assessed the association between inflammatory markers and micronutrients in COVID-19 patients with infection severity and T2DM. Keywords used and search-term combinations were as follows: ("COVID-19"[Mesh] OR "COVID-19"[tiab] OR "SARS-CoV-2"[tiab]) AND ("Type 2 Diabetes Mellitus"[Mesh] OR "T2DM"[tiab] OR "diabetes"[tiab]) AND ("Inflammation"[Mesh] OR "Interleukins"[Mesh] OR "cytokines"[tiab]) AND ("Micronutrients"[Mesh] OR "vitamin D"[tiab] OR "vitamin C"[tiab] OR zinc[tiab] OR copper[tiab]). This review article mainly included observational studies (cross-sectional and prospective or retrospective cohort study) as well as review articles. Scientific articles, systematic reviews, and meta-analyses published in English were included. Studies with insufficient information, as well as letters and comments, were not eligible for inclusion in the current study. Editorial articles were also excluded.

RESULTS

C-reactive Protein

C-reactive protein (CRP) is an acute phase protein mainly produced by the liver in response to stimulation of adipocyte-derived pro-inflammatory cytokines, including IL-6 and TNF-α. CRP is associated with inflammation, and its production is considered a function of innate immunity. This marker can stimulate phagocytosis and promote the killing of pathogenic microorganisms. Its levels elevate with the severity of inflammation and disease.[13] Studies assessing CRP levels in the early stages of COVID-19 infection have shown that CRP levels are positively associated with lung damage and disease progression.[14,15] Risk factors for diabetes in individuals with diabetes can induce the production of acute-phase proteins under the influence of elevated cytokines. This state, in turn, causes insulin resistance and hyperglycemia, followed by the production of advanced glycation end products (AGEs), oxidative stress, and additional inflammatory cytokines.[8]

D-dimer

D-dimers are small protein fragments formed when fibrin is broken down by plasmin. An increase in D-dimer indicates the occurrence of coagulation activity in the body. When fibrin generation and degradation are increased, plasma D-dimer concentration also rises.[16] The D-dimer test is a well-established clinical assay used to assess conditions such as deep vein thrombosis (DVT), pulmonary embolism (PE), disseminated intravascular coagulation (DIC), and arterial thrombosis. Elevated D-dimer levels may also be observed in physiological or pathological conditions such as pregnancy, cancer, inflammation, trauma, stress disorders, and vasculitis.[17] In COVID-19 infection, abnormalities in the coagulation and anticoagulation cascades lead to worsening lung damage. Evidence suggests that SARS-CoV-2 induces activation of the coagulation cascade and thrombotic effects through severe cytokine release in critical cases.[18,19] DIC and activation of the coagulation system play important roles in the progression of COVID-19, as supported by autopsy findings confirming the presence of fibrin thrombosis.[20] A meta-analysis involving 1807 COVID-19 patients showed that serum D-dimer levels were directly associated with disease severity.[21] Because thrombosis can occur in multiple organs in patients with COVID-19, monitoring D-dimer levels in individuals with severe disease and prethrombotic status may be useful in reducing complications and mortality.

Lactate Dehydrogenase

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme that plays a key role in the anaerobic glycolysis pathway by catalyzing the conversion of L-lactate to pyruvate via nicotinamide adenine dinucleotide (NAD^+).[22] This enzyme is composed of four subunits—two types of polypeptides, M and H—and exists in five isoenzyme forms: LDH-1 (H4), LDH-2 (H3M), LDH-3 (H2M2), LDH-4 (HM3) and LDH-5 (M4).[23] *LDH-1* and *LDH-2* are primarily expressed in the heart, kidneys and red blood cells,[24] while *LDH-4* and *LDH-5* are predominant in the liver and skeletal muscles; *LDH-3* is common in lung tissue.[24] A systematic review study including 10 399 COVID-19 patients from 21 studies reported that increased LDH levels were associated with poor clinical outcomes and diabetes.[25] LDH levels are elevated in COVID-19 patients[26] and associated with disease severity.[27] However, some studies suggest that

LDH is not consistently related to poor prognosis.[28] In one case-control study, LDH concentrations were measured in 17 COVID-19 patients, and LDH isoenzymes were assessed using agarose gel electrophoresis. The results showed that total LDH activity was significantly higher in patients than in controls ($p<0.001$). However, no significant differences were detected between patients and controls regarding the in-gel relative activity of LDH isoenzymes (all $p>0.05$). In patients, no meaningful correlations were found between total plasma LDH activity (U/L) and the relative in-gel activity of the different LDH isoenzymes, including the dominant lung-associated form, LDH-3. Likewise, no significant correlations were observed between LDH-3 relative activity and various hematological or serum biochemical markers such as CRP, ferritin, lymphocytes, eosinophils, monocytes.[24] This finding suggests that the increase in plasma LDH commonly observed in COVID-19 patients is not due to a specific elevation of the LDH-3 isoenzyme, which is predominant in the lung. Furthermore, none of the other LDH isoenzymes appear to play a major role in the overall increase of total plasma LDH levels in COVID-19 patients.

Procalcitonin

Procalcitonin (PCT) is a glycoprotein prohormone of calcitonin that is secreted by the parafollicular cells of the thyroid gland.[29] It can also be released by extra-thyroid tissues in response to stimulation by inflammatory cytokines and endotoxins.[30] Although PCT widely used as a biomarker for bacterial infections, its effectiveness as a prognostic marker for COVID-19 remains controversial.[31,32] Some studies, however, have reported a positive association between elevated serum PCT levels and poor outcomes in COVID-19 patients.[33] In vitro studies have shown that parenchymal cells, including adipocytes, can produce procalcitonin in response to macrophages stimulation. Because obesity is associated with an increased presence of activated macrophages in adipose tissue,[34] a similar mechanism may occur in obese individuals. Furthermore, it has been reported that correction of plasma glucose levels leads to a decrease in PCT concentrations in patients with acute hyperglycemia.[35]

Proinflammatory Cytokines

Interleukin-6

IL-6 acts in both pro-inflammatory and anti- inflammatory pathways.[36] In COVID-19, it has been reported to be elevated in patients transitioning from mild to severe.[37] The findings suggest that patients with severe conditions are further prone to cytokine storms, which can be exacerbated by an increase in IL-2, IL-7, G-CSF, TNF-α, and IL-6. This inflammation can lead to death due to pneumonia.[38] IL-6 levels and total computed tomography (CT) scores (≥16) were identified as independent risk factors for poor prognosis in COVID-19 patients, as examined by Zhou et al.[39] Increased levels of this cytokine in severe patients may be useful as prognosis biomarkers and direct treatment strategies.[40] Excessive IL-6 production contributes to pathological inflammation, whereas physiological levels are necessary for host defense.[41] Multiple mechanisms contribute to endothelial dysfunction and lung injury in T2DM patients. Inflammation has been suggested as a cause. One of these small vascular endothelial inflammatory pathways is IL-6, known as a biomarker for inflammatory and metabolic disorders, and a predictor of lung disease.[42]

Interleukin-1

IL-1 is active in innate and adaptive immunity. This marker acts on immune cells (macrophages and mast cells [MCs]) through the expression of some cytokine genes and stimulates IL-6 and TNF-α secretion. Furthermore, IL-1 increases the production of nitric oxide and prostaglandins, and thromboxane A2 is released.[43] Diagnosis of the bilateral lobular pneumonia in the lung CT scan of a COVID-19 patient was correlated with increased levels of IL-1β at early plasma concentrations.[44] Chronic hyperglycemia, a condition associated with T2DM, is detrimental to pancreatic β cells and impairs insulin secretion. The hypothesis that IL-1β may mediate the harmful effects of high glucose on human β cells was investigated by Kathrin Maedler et al,[43] in condition of in vitro. It was observed that, glucose increased the production and release of IL-1β from pancreatic beta cells. Additionally, it activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), upregulates *Fas*, and induces DNA fragmentation and β-cell dysfunction.[45,46] On the other hand, the in vitro study found that, high glucose levels prevented the release of IL-1 (but not its production) by macrophages in RAW 264.7 cells, and this inhibition was mediated by PKC activation.

Interferons

Interferons are classified into three types: type I, type II, and type III. Type I interferons include interferon-α and interferon-β, which are the most prominent members of this group. Type II interferon consists of interferon-γ, while type III interferons are known as interferon-λ. IFN-α is mainly generated by virus-infected leukocytes and interferon-β by fibroblasts.[47] Interferon type II (IFN-γ) is generated by macrophages and natural killer cells (NK cells), as well as T helper clusters of differentiation 4 ($CD4^+$) cells and cytotoxic T lymphocytes $CD8^+$.[47] The higher the viral load, the higher the IFN-γ levels in COVID-19 infections.[44] In SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) elevated IFN-γ amounts were related to pneumonia and widespread lung damage.[48] In antiviral response NF-κB and (interferon regulatory factor) IRF3 are transferred to the nucleus, then these activate interferon type I (*IFN-I*) and other inflammatory cytokines expression, thus creating precedent line of defense against the virus, interferon type I (IFN-I), binding to the interferon-α/β receptor (IFNAR), activates the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway, then phosphorylates STATs 1 and 2 to form an IRF9 complex that transcribes certain genes.[49] Proper functioning of the IFN-I response can suppress virus replication in the early stages. Both SARS-CoV and MERS-CoV employ a variety of procedure to block pathways leading to IFN-I generation and/or IFNAR downstream signaling, and this suppression is directly related to disease intensity.[50] It is suspected that COVID-19 employs similar strategies to regulate the innate immune response, particularly in attenuating the IFN-I response.[50] In fact, delayed IFN-I jeopardizes primary viral control and leads to an invasion of inflammatory neutrophils, monocytes and macrophages. Viral active replication later leads to increased production of IFN-I and an invasion of neutrophils and macrophages. Recently studies have reported the relationship between obesity and immune system disorders.[51,52] Because of the obesity is an important risk factor for type 2 diabetes, nowadays, an important etiology that causes insulin resistance is considered to be innate and adaptive immunity.[53] Th1 cells are, differentiated $CD4^+$ T cells that producing pro inflammatory IFN-γ.[54] $CD4^+$ T cells had polarized to pro inflammatory T helper (Th1 and Th17) cells but polarization to anti-inflammatory Th2 cells decreased in patients with T2DM.[55] In other study Th1/Th2 ratio and levels of cytokines (IL-13, IL-10, IL-4 and IFN-γ) were considerably increased in T2DM patients.[56]

Tumor Necrosis Factor-α

TNF-α is generated by macrophages, monocytes, neutrophils, active lymphocytes, endothelial cells, smooth muscle cells, astrocytes, and fats.[47] TNF-α plays a major role in cytokine storm, It increases earlier in the infection and stays high during it.[57] Studies evaluating intensive care unit ICU and non-ICU patients indicated that TNF-α, IL-2, IL-7, and IL-10 levels were higher in patients admitted to the ICU.[44] TNF-α can cause production of hyaluronan synthase 2 (HAS2) in the alveolar epithelium of the lungs $EpCAM^+$, the alveolar endothelium of the lungs $CD31^+$ and fibroblasts.[58] Hyaluronan (HA) is the main responsible for the invasion of fluid into the alveoli of the lungs, which is mainly cause of deoxygenation and closure of the respiratory tract. TNF-α was very effective in initiating inflammatory pathways, that is, it increases in the early stages of the disease. Anti-TNF-α therapy can create a suitable therapeutic target to prevent the effect of inflammation on various tissues of the body.[59] Early intervention is preferable to late intervention, this treatment way in addition to suppressing TNF-α, also suppresses further inflammatory cytokines consist of IL-6 and IL-1 in animal patterns of sepsis and rheumatoid arthritis. Bertin et al[60] showed that plasma TNF-α levels were associated with body mass index (BMI) ($p<0.02$). The finding of other study indicates that, increased TNF-α levels were associated with the combined effect of obesity and diabetes because serum TNF-α levels in diabetic patients were associated with levels of insulin resistance and hemoglobin A1c (HA1c).[61]

Micronutrients

Vitamin D and Immune Regulation in COVID-19

Vitamin D deficiency is prevalent, affecting approximately half of the US population. It is more common among individuals with darker skin, those with limited sunlight exposure, and older adults. The effect of vitamin D on boosting the immune response in prior coronaviruses has been extensively evaluated and well accepted.[62-64] In fact, when vitamin D receptors are expressed in immune cells, this approach, helps adjust the immune response. In the innate immune system, vitamin D inhibits dendritic cell maturation and prevents the delivery of antigen to T helper cells. It also differentiates macrophages. In adaptive immunity, it

inhibits Th1 and Th17 cells and induces Th2 cells, promoting the growth of regulatory T cells (Treg cell) and inhibiting the release of IL-6 and other inflammatory cytokines.[65] Vitamin D can inhibit cytokine storms, which may help prevent severe COVID-19 infection.[66,67] Vitamin D decreases the generation of interferon-γ and TNF-α factor.[68] The virus can attack various cellular organelles (nucleus, mitochondria, endoplasmic reticulum, peroxisome, etc.) to provide living conditions and intracellular proliferation.[69] Vitamin D functions as a powerful antioxidant, affecting mitochondrial performance. For instance, it has an antioxidant effect by inhibiting NF-κB production and reducing oxidative stress. Active vitamin D binds to the vitamin D receptor (VDR) in monocytes, dendritic cells, and T cells, suppressing pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ, IL-17) while promoting anti-inflammatory signals (IL-10, TGF-β). The mechanisms involve VDR-mediated inhibition of NF-κB and induction of MAPK phosphatases, which blunt p38 MAPK signaling.[70] Relationship between high blood pressure and *ACE2* expression to vitamin D have been extensively examined.[71-73] Data indicate a risk of intense illness in diabetic and hypertensive individual with COVID-19,[74] hypertension in COVID-19 patients marked by renin-angiotensin pathway activated in the lung,[62] the incidence of type 2 diabetes has been recovered to have association with vitamin D-deficiency.[75] Vitamin D receptors are also present in pancreatic cells. Observations from animal models indicate that pancreatic insulin secretion is inhibited by vitamin D deficiency. There is sufficient evidence of a relationship between diabetes and COVID-19, which is more pronounced in the presence of vitamin D levels below 10 ng/mL[76] (Figure 3).

Antioxidant and Immunomodulatory Functions of Vitamin C in COVID-19

Vitamin C is an essential nutrient, known as an enzymatic cofactor. Vitamin C, by enhancing the proliferation of T lymphocytes and the function of NK cells, may ameliorate the immune response against viral infections.[77-80] Vitamin C appears to accumulate intracellularly in neutrophils, which may indicate that vitamin C maintains leukocyte function.[81] Vitamin C adjusts the release of many inflammatory mediators, such as the generation of interferon. Vitamin C reduces the production of certain pro-inflammatory cytokines (e.g., IL-6) in both clinical and experimental settings and can enhance antiviral type I interferon responses in some models. Overall, it tends to suppress hyperinflammatory cytokine release while supporting appropriate innate antiviral signaling.[80] Evidence shows that vitamin C acts as an antioxidant in the body. In addition to directly scavenging free radicals, it also acts as a regenerator of other antioxidants such as vitamin E and tetrahydrobiopterin.[82] Inflammatory and pro-oxidant conditions are the basic pathological processes that cause lung damage and ARDS. Vitamin C defends the lungs against oxidative stress, performing this function by sustaining the integrity of the cells' redox balance, and eventually stopping ARDS.[83] High doses of intravenous (IV) vitamin C decreased the chances of cytokine storm occurrence in the final stages of new COVID-19 infection.[84] A meta-analysis involving 1766 patients showed that vitamin C decreased the duration of ICU stay by about 8%.[85] It may be reasonable to assess vitamin C status in ICU patients and to prescribe it in deficiency terms. Patients in critical condition need large amounts of vitamin C (2–3 g/day).[86] In patients with respiratory viral infections, 6–8 g/day of oral vitamin C is more useful than 3–4 g/day.[87] Glucose may compete with vitamin C for cellular uptake in cells because of its constructional likeness to the vitamin C oxidized form (dehydroascorbic acid).

Role of Zinc in Immunity and Metabolic Regulation During COVID-19

Zinc is an essential trace element crucial for immune function, cellular processes, and insulin regulation. Zinc functions as a signaling ion; transient changes in free Zn^{2+} levels modulate intracellular pathways downstream of Toll-like receptors (TLRs) and T-cell receptors. Adequate zinc helps limit exaggerated pro-inflammatory signaling (e.g., through inhibition of NF-κB activation in some contexts), whereas zinc deficiency is associated with elevated IL-6 and TNF-α levels and with impaired antiviral and antibacterial responses.[88] Zinc deficiency, caused by factors such as geography, nutrition, and disease (e.g., chronic viral infections), weakens immune responses, impairing phagocytosis, cytokine production, and T-cell development.[89] This element stimulates the production of IFN-γ and IL-12. The role of IL-12 is to activate NK cells and cytotoxic T cells, and both IL-12 and IFN-γ play a significant role in the destruction of pathogens.[4,90] In COVID-19, zinc levels significantly decrease with disease severity, correlating with higher

CRP levels. Zinc deficiency also contributes to increased inflammation and increased susceptibility to viral infections. Zinc is vital for insulin storage in the pancreas, and its deficiency is linked to diabetes, as evidenced by reduced insulin and zinc levels in diabetic patients.[91] Zinc transport into β-cells is regulated by zinc transporters (ZnT and ZIP proteins), which play a key role in insulin secretion. Alterations in these transporters, particularly ZnT8, are associated with type 1 and T2DM. Zinc-α2-glycoprotein (ZAG) enhances glucose uptake and energy utilization, further highlighting zinc's role in metabolic health.[92]

Antiviral and Immunomodulatory Properties of Copper in COVID-19

Copper (Cu) is an essential trace element that acts as a cofactor of enzymes in the redox chemistry of enzymes, mitochondrial respiration, iron absorption, and free radical scavenging.[93] Subsequently, the utilization of Cu in antioxidant and anti-inflammatory pathways will reduce its serum content. Besides, severe copper deficiency is associated with inheritance, nutrition, geography, socioeconomic status, and certain chronic pathological conditions. Cu indicates antiviral activity, which may be reasonable, by effect of Cu on injury to the viral membrane. Another antiviral action of Cu, includes binding to genome strands, leading to damage of the virus's genomic DNA, as well as limiting its metabolism, respiration, and reproductive processes. Cu prevents polymerase activity more effectively than other metal ions. Increasing serum Cu level happens in answer to inflammation, Cu may suppress the production of inflammatory cytokines by downregulating the expression of *NF-κB* (mostly stimulated by virus-induced ROS). In the blood ceruloplasmin (CP) acts as a transporter protein for Cu; both Cu and CP are involved in a positive acute phase reaction. Through the Fenton reaction, Cu, under non-protein-binding conditions, can produce reactive oxygen species that are harmful to tissues or cells.[94]

The relationship between inflammatory markers, micronutrients, and their immunological effects in COVID-19 is summarized in Table 1.

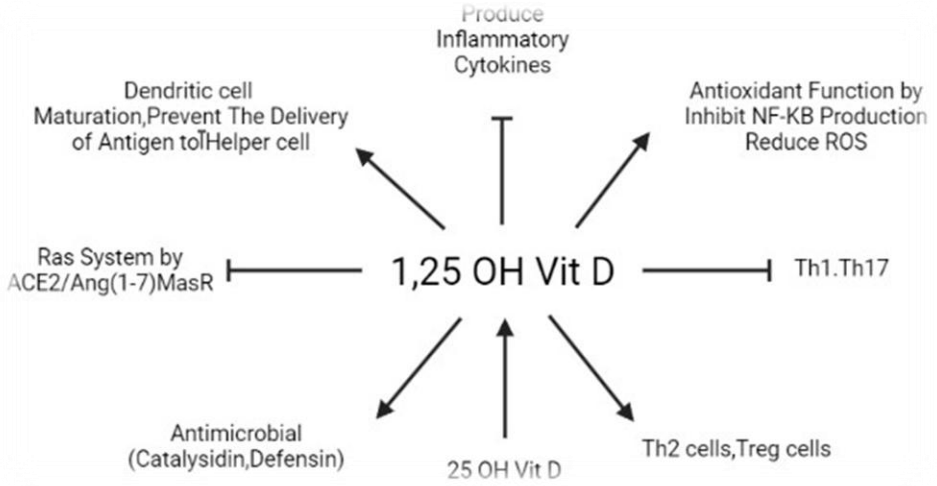


Figure 3. Role of 1,25-dihydroxyvitamin D (1,25 OH vit D) in immune regulation and cellular function. One of the key actions of 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] is the regulation of inflammatory cytokine production, thereby limiting excessive immune activation and maintaining immune homeostasis. Additionally, 1,25(OH)$_2$D exhibits antioxidant properties by inhibiting NF-κB activation and reducing reactive oxygen species (ROS), helping to prevent oxidative stress and tissue damage. In adaptive immunity, 1,25(OH)$_2$D promotes the development of Th2 and regulatory T (Treg) cells, which contribute to anti-inflammatory responses and immune tolerance, while suppressing Th1 and Th17 cells, which are typically involved in pro-inflammatory and autoimmune pathways. It also modulates dendritic cell maturation, preventing these antigen-presenting cells from activating T helper cells and further limiting immune overactivation. Within the innate immune system, 1,25(OH)$_2$D enhances antimicrobial defense by stimulating the production of natural antimicrobial peptides such as cathelicidin and defensins, which protect against pathogens. Moreover, it interacts with the renin-angiotensin system (RAS) via the ACE2/Ang(1-7)/MasR pathway, influencing both cardiovascular and immune regulatory functions. Finally, 1,25(OH)$_2$D is derived from its precursor, 25-hydroxyvitamin D [25(OH)D], directly linking its actions to vitamin D metabolism and status.

Table 1. Inflammatory markers, micronutrients, and their immunological effects in COVID-19.

Marker / Micronutrient	Typical change in COVID-19	Immunological / mechanistic effect	Clinical associations / notes
IL-6[42,95]	↑ (higher in severe/complicated cases)	Pleiotropic cytokine: stimulates acute-phase reactants (e.g., CRP), promotes neutrophil/monocyte recruitment, and influences T-cell and B-cell differentiation.	Elevated IL-6 correlates with severity, ICU admission, and worse outcomes. Also implicated in "cytokine storm" phenomena.
IL-1 family (especially IL-1β)[96]	↑ in many severe cases, though data somewhat variable	Key inflammasome-driven cytokine, promotes endothelial activation, neutrophil recruitment, can trigger downstream IL-6 release.	Elevated IL-1 family cytokines may contribute to hyperinflammation in severe COVID-19; yet some studies show no large difference in IL-1β levels.
IFN-γ[97]	Mixed: some studies show ↑ in fatal cases; others show impaired early IFN responses.	Important Th1 cytokine: activates macrophages, supports $CD8^+$ T cell cytotoxicity, NK-cells. In SARS-CoV-2, early strong IFN response may help viral clearance; dysregulation may lead to pathology.	Higher IFN-γ associated with mortality in one study. But severe cases may have blunted IFN responses initially.
TNF-α[97]	↑ In many severe cases; in combination with IFN-γ drives macrophage activation/phenotype.	Potent pro-inflammatory cytokine: promotes endothelial activation, leukocyte adhesion, can contribute to cell death, tissue damage, vascular leakage. In COVID-19.	Elevated TNF-α linked to worse immune activation and outcomes.
CRP[98]	↑ (acute-phase reactant) in COVID-19; higher in severe cases.	Produced by liver in response to IL-6; indicates systemic inflammation rather than specific antiviral immunity.	High CRP correlates with severity, ICU admission, and poor outcomes. May help prognostication.
LDH[99]	↑ In severe disease; higher in non-survivors.	A marker of tissue damage/cell death elevated levels may reflect greater tissue injury and immune dysregulation.	Elevated LDH independently predicts severity, ICU/ARDS, mortality.
PCT[100]	↑ (though often modest) in severe COVID-19; more marked if bacterial co-infection.	Normally marker more specific to bacterial infection, but in COVID-19 may rise in systemic inflammation or secondary infection.	Elevated PCT associated with worse prognosis but must interpret in context (e.g., bacterial superinfection).
D-dimer[101]	↑ (often substantially) in more severe/critical illness.	Marker of fibrin degradation indicates activation of coagulation/fibrinolysis system; in COVID-19 reflective of endothelial injury + prothrombotic state.	Elevated D-dimer strongly linked to thrombotic complications, ICU need, and mortality.
Vitamin D (25-OH-D)[102]	Often low/deficient status observed in patients with severe COVID-19. Some but not all studies show associations.	Immune-modulatory: Vitamin D receptor expressed on immune cells (macrophages, T cells, B cells). It may suppress excessive pro-inflammatory cytokine production (e.g., IL-6, TNF-α) and support innate antiviral responses.	Meta-analyses/intervention studies show mixed results; supplementation may reduce intubation but not consistent mortality benefit.

Table 1. Continued...

Marker / Micronutrient	Typical change in COVID-19	Immunological / mechanistic effect	Clinical associations / notes
Vitamin C (ascorbic acid)[103,104]	Often lower levels in critical illness (not unique to COVID). Some supplementation trials done.	Antioxidant, supports neutrophil function, endothelial integrity, may reduce oxidative stress and vascular damage in viral infections.	RCT data in COVID-19 for vitamin C show inconsistent results; not definitive.
Zinc[105,106]	Deficiency more common in older/comorbid patients; limited causality evidence.	Zinc is essential for innate and adaptive immunity (NK cells, T cells), influences viral replication, and may modulate cytokine production.	Observational links to better outcomes in some cohorts, but causality not proven; supplementation benefit uncertain.
Copper[107,108]	Some observational studies but causality not established.	Copper is involved in immune cell function, oxidant/antioxidant enzymes, and may influence viral replication; excessive or deficient copper could modulate immune response.	Limited specific COVID-19 interventional data.

ARDS: acute respiratory distress syndrome; CD: cluster of differentiation; CRP: C-reactive protein; ICU: intensive care unit; IFN: interferon; IL: interleukin; LDH: lactate dehydrogenase; NK: natural killer; PCT: procalcitonin; RCT: randomized clinical trial; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; Th: T helper; TNF: tumor necrosis factor.

DISCUSSION

COVID-19 has posed a major global health challenge, with disease severity ranging from mild, self-limiting illness to critical multisystem involvement and death. Identifying reliable biomarkers for disease severity and therapeutic monitoring has therefore been a central focus of clinical research. In this context, inflammatory markers and micronutrients have emerged as important indicators of immune dysregulation and metabolic vulnerability. Type 2 diabetes mellitus has received particular attention as a major comorbidity associated with adverse COVID-19 outcomes, owing to chronic inflammation, impaired immune responses, and altered expression and glycation of *ACE2*.

Diabetic patients are prone to infections (e.g., foot infections, diabetic ketoacidosis). Procalcitonin is useful for distinguishing bacterial infections from non-infectious inflammation in diabetic contexts; however, severe sterile inflammation can also elevate PCT levels. Therefore, in diabetes, an increased PCT level primarily indicates a bacterial infection or a severe systemic inflammatory response, which often coexists with elevated CRP, LDH, and D-dimer levels.[109] Evidence shows that CRP, LDH, and D-dimer levels are frequently elevated in individuals with diabetes who contract COVID-19 and tend to correlate with greater disease severity. In contrast, findings regarding PCT are more inconsistent; PCT levels often rise in severe COVID-19 but may reflect bacterial coinfection or late-stage disease rather than diabetes itself. Some studies include only hospitalized (severe) patients, whereas others involve outpatients or mixed cohorts. Because biomarker levels increase with disease severity, studies with a higher proportion of severe cases tend to show stronger associations.[110] In COVID-19 infection, abnormalities in the coagulation/anticoagulation cascade led to worsening lung damage. A study in Wuhan, China, found an important association between D-dimer and the severity of COVID-19 infection. It is not clear whether this is a direct effect of the virus or is caused by an inflammatory process.[111] A systematic review study including 10 399 COVID-19 patients from 21 studies was conducted. The results indicated that increased LDH levels were related to poor outcomes and diabetes.[25] IL-1 findings are mixed: while some genetic or polymorphism studies and small clinical series suggest involvement of the IL-1 pathway in disease severity, large studies have not consistently demonstrated significant serum-level associations in

diabetic COVID-19 cohorts.[112] IL-1β induces the expression of additional proinflammatory mediators (such as *IL-6* and various chemokines) in β-cells and recruits immune cells, creating a self-amplifying loop that accelerates β-cell failure in type 2 diabetes and contributes to islet inflammation in type 1 diabetes (T1D) contexts.[113] PCT is widely used as a biomarker of bacterial infection; however, there are conflicting views on the effectiveness of PCT as a prognostic marker for COVID-19.[31,32] Some assessments confirmed the positive relation between serum PCT levels and bad outcomes in COVID-19.[33] According to Lippi et al,[33] a fivefold increase in PCT levels is expected in severe cases of COVID-19.[37,39] However, based on the findings of Zhao et al,[46] increased levels of IL-6, IL-12, IL-1β, IFN-γ, IL-17, and IL-27 in severe cases of COVID-19 were observed only in the final stages, mainly 4 weeks after the onset of symptoms. In response to viral infection, the effect of innate immune via IFN-I production is critical, and then reaches its peak in adjustment virus replication and inducing adaptive immune response.[114]

Type I interferon signaling is frequently reported as impaired in severe COVID-19, often co-occurring with hyperinflammation. This pattern has also been described in some diabetic cohorts, although other studies have reported elevated IFN-γ (type II IFN) levels during certain phases, such as long COVID or specific disease phenotypes. Advanced glycation end-products (AGEs) accumulate in diabetes and bind to the receptor for AGEs (RAGE) on immune and stromal cells, activating NF-κB and JAK–STAT pathways and their downstream inflammatory cascades.

AGE–RAGE signaling can enhance proinflammatory cytokine programs-including those of the IFN family-in local tissues and peripheral blood mononuclear cells (PBMCs), depending on ligand context and cell type. In other contexts, chronic exposure to AGEs leads to immune dysfunction or exhaustion and impaired cytokine responses.[115] TNF-α increases earlier in the infection and stays high during it.[57] Many studies report higher circulating IL-6 and TNF-α levels in individuals with diabetes who develop COVID-19, linking these cytokines to worse outcomes. However, not all studies observe the same magnitude of elevation or prognostic value. Elevated glucose induces oxidative stress in monocytes/macrophages and endothelial cells, with reactive oxygen species (ROS) activating NF-κB and MAPK pathways, thereby increasing *IL-6* gene expression and secretion. This effect occurs both after acute hyperglycemia and with chronic exposure. TNF-α activates kinases such as JNK and IKK, which phosphorylate insulin receptor substrates (IRS-1/2) on serine residues, impairing insulin signal transduction via reduced PI3K/Akt signaling. TNF-α also promotes lipolysis, increases free fatty acids, and enhances hepatic glucose production, collectively contributing to insulin resistance. Vitamin D exerts antioxidant effects by inhibiting NF-κB activation and reducing oxidative stress, and it may help prevent severe COVID-19 by mitigating cytokine storms.[66,67] Observational studies indicate that lower 25-hydroxyvitamin D [25(OH)D] levels are associated with increased risk of infection, hospitalization, and poorer outcomes. Randomized controlled trials and meta-analyses report heterogeneous effects: some show reductions in ICU admissions or disease severity in certain analyses, but a consistent mortality benefit has not been observed. The potential benefit appears greater when deficiency is corrected, rather than by administering high doses to individuals with normal vitamin D levels. Chronic hyperglycemia and kidney damage downregulate renal 1α-hydroxylase activity and impair reabsorption, thereby reducing production of active 1,25-dihydroxyvitamin D [$1,25(OH)_2D$].[116] Low-grade inflammation reduces circulating 25(OH)D levels and alters vitamin D receptor (VDR) signaling. Hyperglycemia and osmotic diuresis increase renal excretion of water-soluble vitamins; several studies have documented enhanced urinary loss of ascorbate in individuals with diabetes, leading to lower plasma vitamin C levels.[117] Diabetes represents a pro-oxidant state, characterized by chronic ROS production from mitochondria, glycation, and NADPH oxidases. Ascorbate is consumed more rapidly in this context, acting as a major antioxidant and cofactor.

Neutrophilia is observed in COVID-19 infections. Zinc gluconate supplementation reduces neutrophil infiltration into the airways and can also inhibit TNF-α release by blocking the transcription of NF-κB-dependent inflammatory genes.[91] In vitro, zinc deficiency increases the generation of IL-6 and IL-1B.[118] In a study investigating the association between serum zinc concentration and COVID-19 severity, a significant relationship was observed between lower zinc levels and greater disease severity. This finding highlights the importance of monitoring serum zinc concentrations in patients with COVID-19. Zinc possesses plausible

antiviral and immunomodulatory properties; however, prolonged high-dose supplementation can lead to adverse effects, particularly copper deficiency.[119] Osmotic diuresis and tubular dysfunction increase urinary zinc excretion, leading many diabetic patients to exhibit lower serum and intracellular zinc levels. During chronic inflammation in diabetes, zinc is redistributed from plasma into the liver and immune cells as part of the acute-phase response, resulting in reduced serum zinc concentrations.[120] High levels of Cu can have a toxic effect due to its redox reactions. Higher levels of Cu have been reported at sites of lung infection. Therefore, excessive and low levels of Cu lead to destruction of immune function.[121] The study conducted in Moscow on the relationship between the severity of COVID-19and metal elements such as Cu and Zn (in 3 groups of patients with mild, moderate and severe disease), the results indicate that the serum level of Cu has a positive relationship with the severity of the disease, but zinc levels are negatively related to disease severity, and the Cu/Zn ratio is a good predictor of low SPO2 in COVID-19.[107]

CONCLUSIONS

The findings of this review highlight the critical role of inflammatory markers and micronutrients in determining the severity and progression of COVID-19, particularly among patients with type 2 diabetes. Elevated inflammatory cytokines, along with dysregulated levels of vitamins D and C, zinc, and copper, may exacerbate immune dysfunction and worsen clinical outcomes in this population. These insights underscore the importance of routine monitoring of inflammatory and nutritional biomarkers in diabetic patients with COVID-19 to support early intervention and optimize treatment strategies. Future research should focus on elucidating the mechanistic pathways linking inflammation, micronutrient status, and glycemic control to COVID-19 severity, as well as on evaluating targeted nutritional and anti-inflammatory therapies to improve patient outcomes.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee in Research of the Tabriz University of Medical Science (IR.TBZMED.REC.1403.785).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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