




# Nutritional management of diabetes mellitus during the pandemic of COVID-19: a comprehensive narrative review

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## Abstract

**Objectives** According to the recent epidemiological studies, patients with diabetes mellitus (DM) may be at higher risk of hospitalization due to COVID-19. Regarding the important role of nutrition on the immunity, the present review article aimed to outline nutritional support of DM during the outbreak of COVID-19 with a mechanistic insight.

**Methods** Searches were performed in PubMed/MEDLINE, ScienceDirect, Scopus, and Google Scholar databases from 2000 until December 2020 using the following keywords. All relevant clinical and experimental studies published in English were included.

**Results** Evidences revealed that hyperglycemia is a significant predictor of some viral infections including COVID-19 which can exacerbate the complications of DM. According to the literature review, adequate intake of dietary protein, fiber, essential fatty acids and some micronutrients especially vitamins D, C, B12, folate, zinc and selenium has beneficial effects on the prevention and treatment of COVID-19 in diabetic patients through modulation of innate and adaptive immune responses or direct effects on virus enzymes or the rate of cell entrance.

**Conclusions** It is well understood that malnutrition may increase susceptibility to viral infections and disease progression. Therefore, considering nutritional status of diabetic patients and reasonable supplementation of the above mentioned nutrients can ameliorate the symptoms of COVID-19 in DM. However, further well-designed clinical trials are needed to determine their therapeutic dose.

**Keywords** COVID-19 · Immunity · Diabetes mellitus · Nutrition · Protein · Carbohydrate · Selenium

## Introduction

Nowadays, the novel coronavirus (COVID-19) is the main health care problem around the world [1]. According to the latest statistics of World Health Organization (WHO), there are more than 86 million confirmed COVID-19 cases and more than 1.5 million deaths around the world [2]. Clinical manifestations of COVID-19 range from mild symptoms to critical illness and death [3, 4]. Frequently reported symptoms of infected patients include fever (77–98 %), cough (46–82 %), myalgia or fatigue (11–52 %), and difficulty of breath (3–31 %) at the onset of illness, which can progress to severe lung injury and severe respiratory distress syndrome [3, 5–7]. It was reported that the virus entry in to the alveolar epithelial cells may be through the angiotensin-converting enzyme-2 (ACE2) receptor which can cause severe lung inflammation and acute respiratory distress syndrome (ARDS) [8–10].

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Available researches indicated that older adults and people with underlying diseases including diabetes mellitus (DM), cardiovascular disease, hypertension, lung disease and cancer are at higher risk and more prone to the infection [11–14].

It was reported that patients with DM have had higher morbidity and mortality rates of COVID-19. According to a recent systematic review, the incidence rate of COVID-19 in diabetic patients was 14 % [15]. Docherty et al., reported that among 20,133 hospitalized patients with severe COVID-19 in the UK, the prevalence of DM was 21 % [16]. Moreover, Riddle et al., reported that among 44,672 patients in China with confirmed COVID-19, the mortality rate of diabetics was 7.3 %, which was more than three times that of the overall population [17]. Another study in the UK reported that the mortality risk of diabetics with COVID-19 can be up to 2–3 times greater than non-diabetic patients [18]. However, Fadini et al., indicated that DM may not increase the risk of COVID-19 incidence but can worsen its outcome and severity of the infection [19]. According to the epidemiological studies, DM increases the risk of hospitalization, critical care requirement and also mortality rate due to COVID-19 [20–22].

Therefore, it seems that diabetic patients need special attention during the pandemic of COVID-19.

Diabetes is a chronic inflammatory condition that can affect immune response to pathogens [22]. Hyperglycemia promotes secretion of pro-inflammatory cytokines and glycosylation end products (AGEs) which makes patients vulnerable to the infections [23, 24]. In addition, over production of free radicals after viral infection can exacerbate the oxidative stress in diabetics and leads to the intrapulmonary oxidative injury and lung inflammation [19].

It is well understood that malnutrition may affect the consequences of viral infections and also its pathogenicity [23–28]. Researchers indicate that host nutritional status not only affects the immune function of the body, but also may have some direct effects on the viral genome and its virulence [29]. Therefore, considering nutritional status of people, especially most vulnerable patients like diabetics during the outbreak of novel coronavirus is very important. In this regard, the present review article aimed to outline nutritional support for the prevention and treatment of COVID-19 in diabetic patients, with a focus on nutrients' mechanisms of action.

## Methods

Searches were performed in PubMed/MEDLINE, ScienceDirect, Scopus, and Google Scholar databases from 2000 until December 2020 using the following keywords based on MeSH terms. Generally, a topic-centric search was conducted to write each section. We included all relevant clinical and experimental studies which were the closest to our keywords and published in English. The search terms

included “immunity” OR “viral infection” OR “COVID-19” AND “diabetes” AND/OR “nutrition” OR “antioxidant”; “vitamin D”; “vitamin A”; “vitamin C”; “folic acid”; “zinc”; “selenium”; “macronutrient “. These search items were used for the relevant sections of the review.

As the number of studies on nutritional support of COVID-19 and diabetes mellitus is very limited, we included all related antiviral nutrients along with recent reports regarding their effects on COVID-19 and diabetes mellitus. Data were extracted from the included manuscripts by one author (SM). Two other authors checked the accuracy of the data extracted (VEA, MSA). Some of the related studies are mentioned in the Table 1.

## Results and discussion

### Macronutrients

#### Carbohydrates

It was reported that hyperglycemia is a significant predictor of some viral infections including H1N1 [39], SARS-COV [40] and MERS-COV [41]. Moreover, it seems that there is a bilateral association between blood sugar and infection. A recent study demonstrated increased secretion of glucocorticoids and catecholamines, insulin resistance and increased blood glucose levels after infection with COVID-19 which can exacerbate diabetic complications [42]. Therefore, it is important to pay attention to the glycemic control of viral-infected patients especially those with DM.

Diabetic patients with mild to moderate COVID-19 symptoms need a balanced ratio of carbohydrates intake (45–55 % of calories) mostly as complex carbohydrates and low simple sugars for better glycemic control. In addition, adequate intake of functional fibers (prebiotics such as beta-glucan and fructooligosaccharides) from dietary sources (e.g., oat, wheat, banana, onions, garlic, and tomato) can be helpful through direct effect on gut microbiota and also immune defense system [43–45].

Hospitalized diabetic patients with severe COVID-19 symptoms may need supportive nutrition. Enteral nutrition (EN) is usually well tolerated by the patients and is preferred over parenteral nutrition (PN). Nasogastric or orogastric EN should be initiated within 48 h of admission to the intensive care unit (ICU) [46–48]. The amount of carbohydrate in enteral feeding formula depends on patient's condition (e.g., glycemic control, ventilator dependency) and is usually 30–50 % of non-protein calorie [49]. Generally, it was recommended that glucose should not exceed 5 mg/kg/min [46, 47].

Results of some experimental studies [43, 50] showed that significant restriction of carbohydrates can exacerbate viral

**Table 1** The summary of some recent relevant studies regarding the micronutrients and COVID-19

Authors- Published year	Nutrient	Study population	Study design-aim	Significant outcome
Acosta-Elias et al. 2020 [30]	Folate	Pregnant women	Cross-sectional – Comparing the frequency of infected pregnant women during 2009 H1N1 pandemic and COVID-19 pandemic	A tenfold decrease in the hospitalization due to COVID-19 as compared to H1N1 pandemic may be because the protective effect of folate on SARS-COV-2 through different mechanisms e.g., inactivation of its furin endoprotease enzyme
Narayanan and Nair 2020 [31]	Vit B12	<i>In vitro</i>	A homology modeling study on the inhibition of the activity of nsp12 protein of SARS-COV-2	Vitamin B12 as methylcobalamin may act as an effective inhibitor of the virus's nsp12 protein.
Razzan et al. 2020 [32]	Vitamin D	-	Review article	Supplementation with daily dose of below 4000 IU VitD3 can be beneficial for improving the immune system to combat COVID-19
Reharusum et al. 2020 [33]	Vitamin D	780 confirmed	Retrospective cohort study- Data extraction from electronic medical records.	Vit D status is strongly associated with covid-19 mortality (adjusted for age, sex and comorbidity). Individuals with insufficient and deficient vit D status were respectively 12.55 and 19.12 times more likely to die from the disease
Hiedra et al. 2020 [34]	Vitamin C	Covid-19 infected patients (n= 17) with other comorbidities like DM	Case series- intra-venous vitamin C injection (1 gram every 8 h for 3 days)	A significant decrease in inflammatory markers, the need for mechanical ventilation and mortality rate
Zhang et al. 2020 [35]	selenium	Confirmed cases of COVID-19	Retrospective cohort study- Data extraction from electronic medical records	There were higher pathogenicity or mortality under selenium deficiency (based on hair selenium status)
Moghaddam et al. 2020 [36]	Selenium	COVID-19 patients	Cross sectional study- the assessment of serum Se and survival rate	Higher serum level of selenium was related to increasing survival rate in COVID-19 patients
Mossink JP. 2020 [37]	Zinc	-	Review article	Major high risk groups for COVID-19 including elderly, men (compared to the women), obese individuals and diabetic patients are all at risk of zinc deficiency and as zinc depletion impairs antiviral immunity, it seems that zinc deficiency can increase susceptibility for COVID-19.
Velthuis et al. 2010 [38]	Zinc	<i>In vitro</i>	Experimental study- ero-E6 cells were cultured and infected with SARS-Cov	Zn <sup>2+</sup> efficiently inhibited the RNA-dependent RNA polymerase (RdRp) activity of SARS-COV-2 and also the RNA synthesis

outcomes because the immune cells like CD4 + and CD8 + T cells, involved in pathogen clearance, supply most of their energy from glucose and anaerobic glycolysis [51].

### Protein

Some evidences support the beneficial effects of high protein diets on glycemic control, insulin resistance and maintenance of lean body mass in diabetic people [52]. The amount of protein intake can also directly impact the immune response. It was reported that mice feeding with a low-protein diet, followed by the infection with influenza virus was accompanied by decreased number and function of CD8<sup>+</sup> T cells as well as NK cells, higher viral titers and increased mortality of animals [51, 53]. Therefore, appropriate protein intake of 1.2 to 1.5 g/kg ideal body weight (20–30 % of calories) with at least 50 % from high biological value (HBV) proteins is recommended for almost all people including type 2 diabetic adults and older people to maintain their respiratory muscle strength and support immune function during infection with COVID-19 [54, 55].

In turns of EN for critically ill patients with COVID-19, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommended the protein supply of about 1.2–2.0 g/kg/day for non-obese patients (based on actual body weight) and 2–2.5 g/kg/day for class I– III obese patients (based on ideal body weight) [46–48]. When EN cannot be continued, PN should be prescribed with per case decision making [56].

### Fatty acids

It was reported that the type of dietary fatty acid is very important in the inflammatory and immunomodulatory responses of host to a microbial agent [57, 58]. Adequate intake of omega-3 fatty acids may protect host against viral and bacterial infections [59]. However, there are some controversies regarding the efficacy of omega-3 supplementation in different bacterial and viral infections [60–63]. Patients with DM are more exposed to oxidative stress. Therefore, it is important to consider the quantity and also quality of dietary fatty acids especially during infections and inflammatory condition [64, 65].

COVID-19 can cause severe lung injury and ARDS [66]. In this condition, increasing dietary fat intake helps to decrease CO<sub>2</sub> production as well as ventilator dependency. According to the dietary recommendations for ARDS and pneumonia, an enteral feeding with 30–45 % of calories from fat maybe helpful [67–69]. The amount of fat in EN formula depends on patient's condition (e.g., serum triglyceride, ventilator dependency) and is usually 50–70 % of non-protein calorie [49].

However, regarding the quality of fatty acids, results of two recent systematic reviews showed that there are some controversies toward the benefits of long-chain omega3 fatty acids supplementation on the length of mechanical ventilation and mortality rate in adult patients with ARDS [69, 70]. Overall, adequate intake of essential fatty acids (EFAs) and appropriate proportion of poly unsaturated fatty acids (PUFAs) and mono unsaturated fatty acids (MUFAs) intake can be effective in patients with COVID-19 pneumonia and ARDS symptoms [48, 68, 71]. According to the recommendation of ASPEN for enteral feeding, 500 mg/day eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) might be added to the parenteral feeding requirements of 0.1 to 0.2 g/kg/d [46]. Moreover, the use of omega 6 soy-based intravenous lipid emulsion should be restricted [47].

### Micronutrients

#### Vitamin B12 and B9

Vitamin B12 (VitB12) and vitamin B9 (folate/ folic acid) both act as a human immunity modulator. They can stimulate the T-lymphocytes production, restores the ratio of CD4/CD8 and improve beta-cell function by lowering oxidative stress [71–76]. Low serum levels of folate and B12 in type 2 diabetic patients is correlated with lower circulating level of glutathione and total antioxidant status [77]. Moreover, vitamin B12 supplementation in deficient subjects increased percentage of CD3 and CD7 cells and restored the function of lymphocytes and NK cells [78].

It should be noticed that diabetic patients are more prone to folate and B12 deficiency because of the established drug-nutrient interactions, especially those treated with metformin [79–81].

There is insufficient evidence about the effectiveness of B vitamins in the treatment of COVID-19 and it is not mentioned in the WHO Interim Guidance for COVID-19 management [82]. However, there are some promising reports about benefits of folate and VitB12 regarding the novel coronavirus (SARS-CoV-2).

Recently, Narayanan and Nair suggest that VitB12 can inhibit the RNA-dependent-RNA polymerase activity of the nsp12 molecule from SARS-CoV-2 virus and therefore decrease its pathogenicity and the severity of infection [31]. Two recent studies reported that supplementation with VitB12 may increase the synthesis of melatonin in body which has anti-inflammatory and anti-oxidative effects and may be effective in the treatment of COVID-19 [83, 84].

It was reported that SARS-CoV-2 may interfere with vitamin B12 metabolism and cause clinical manifestation of cobalamin deficiency by impairing the intestinal microbial proliferation. Therefore, it has been suggested that treatment with vitamin B12, especially as methyl cobalamin, can ameliorate

symptoms of COVID-19. Accordingly, supplementation with high doses of VitB12 (1000–2000 µg/day) during the existing deficiency, can be effective [85].

Moreover, there are some recent promising reports of the effectiveness of folic acid on COVID-19. It was shown that folate can inactivate protease 3CLpro, a protein that all the coronaviruses need to replicate, so can reduce the replication of this virus [86, 87]. Two other studies reported that folate can inactivate the furin endoprotease enzyme of SARS-CoV-2 which is crucial for the virus entrance into the host cell [30, 88].

## Vitamin D

Over the past decade, vitamin D (VitD) has attracted substantial interest due to its extra-skeletal functions including immuno-modulatory and anti-inflammatory effects [89–91]. Vitamin D has also some metabolic effects like stimulating insulin secretion and reducing peripheral insulin resistance through vitamin D receptors in the muscles and liver [92–94].

Regarding the immunomodulatory effect of VitD, results of some review articles showed that low circulating level of VitD is related to increased risk of viral respiratory infections [95–97] and VitD supplementation may have protective effects on the respiratory tract infections like influenza virus [98, 99].

In the case of current COVID-19 pandemic, it was suggested that vitamin D-deficient subjects may be more vulnerable to the infection [100] and there is a significant reverse association between serum 25(OH) D level and severity of COVID-19 disease [101]. Moreover, the outbreak of novel coronavirus occurred in winter, the time when 25-hydroxyvitamin D (25(OH) D) concentrations are lowest. Generally, the mortality rate of COVID-19 increases with age and comorbidities like diabetes which are associated with lower VitD concentration [33, 102].

Results of a recent retrospective study indicated that insufficient serum level of VitD was one of the main fatality risk factors related to COVID-19 and VitD insufficient cases were approximately 12.55 times more likely to die after the infection. Moreover, the combination of comorbidities with VitD insufficiency were associated with increasing odds of death [103].

It is established that VitD modulate both innate and adaptive immune responses, B-lymphocytes, monocytes, macrophages, dendritic cells (DCs) and T-cells. Vitamin D can suppress the pro-inflammatory Th1 and Th17 cells and also enhance the regulatory T cells [104]. Along with these immunomodulatory effects, the protective effect of VitD against COVID-19 is also related to the suppression of cytokine response and reduced risk of ARDS [105]. Moreover, VitD supplementation seems to inhibit ACE2, one of the main identified host cell receptors of COVID-19 and consequently helps to attenuate the lung infection [106].

As a preventive strategy, it is recommended to maintain serum level of VitD at sufficient level (> 30 ng/mL) and the goal should be to raise VitD concentrations above 40–60 ng/mL [107]. Overall, it was reported that VitD concentration of 38 ng/mL was appropriate to decrease pneumonia. However, to achieve the above 25(OH) D concentration range, supplementation with 2000–4000 IU/day was recommended especially for people at higher risk of COVID-19 including diabetic patients [32]. However, those health benefits of vitamin D should not be exaggerated and people should skip from toxic overdoses supplementation.

## Vitamin C

Vitamin C (VitC) is a famous antioxidant and also has immune-modulating effects through T-cells transformation, interferon production and phagocytic function [108].

It was reported that patients with severe respiratory infections have lower plasma VitC concentrations so that treatment with VitC restores their plasma VitC levels and ameliorates severity of respiratory symptoms [109]. Hemila et al. demonstrated that the high-dose intravenous VitC infusion (200 mg/kg body weight/day) decreased the duration of hospitalization in severe sepsis and septic shock, along with a significant reduction in the mortality rate [110]. These findings were also reported in patients infected by influenza virus [111, 112].

There are some evidences that vitamin C deficiency is more prevalent in patients with diabetes mellitus compared to the non-diabetic individuals. DM is usually accompanied by increased production of reactive oxygen species (ROS) and decreased level of antioxidant enzymes like superoxide dismutase (SOD) [113, 114]. Numerous studies reported the protective effects of VitC against oxidative damage of diabetes [115, 116].

Nowadays during the pandemic of COVID-19, it has been reported that the markers of inflammation and oxidative stress increase in infected patients and large dose of antioxidants like VitC may be applicable to COVID-19 [117]. A most recent study by Hiedra et al., reported that short term intravenous vitamin C treatment in SARS-CoV-2 positive patients (n = 17) decreased inflammatory markers. Moreover, low mortality rate and the need for mechanical ventilation in this study may be related to VitC treatment. Interestingly, 47 % of those infected patients have diabetes mellitus [34].

To our knowledge, a few clinical trials has recently designed to assess the effect of vitamin C treatment in patients with COVID-19. Their results and also further randomized controlled trials in severe COVID-19 patients especially with the comorbidity of DM could better clarify the possible protective role of vitamin C.

## Selenium

Selenium (Se) plays a functional role in redox hemostasis, hormone metabolism and protection against oxidative stress and inflammation [118]. Low serum level of selenium is related to poor immune function and increased risk of mortality and its deficiency impairs both the innate and acquired immunity [119, 120]. Moreover, some epidemiological studies reported that a high level of serum selenium reduce the prevalence of diabetes and also its chronic complications [121, 122].

Regarding the immunomodulatory effects of Se, it is well documented that selenium deficiency is associated with higher susceptibility to viral infections and their pathogenesis therefore, it seems that Se supplementation may be applicable for COVID-19 [123]. A most recent epidemiological study by Zhang et al., demonstrated a positive correlation between selenium status (based on hair selenium concentration) and the recovery rate of COVID-19 [35].

In another study Moghaddam et al., reported that high serum level of selenium in COVID-19 patients was related to increasing survival rate [36]. It seems that Se inhibits the entrance of different viruses into the cells and prevents their infectivity. Therefore, it may be useful against the pandemic of COVID-19 [124]. Since diabetic patients are susceptible to low anti-oxidative level, Se supplementation might be a helpful choice for the prevention or treatment of diabetic patients infected by novel coronavirus.

## Zinc

Zinc (Zn) has a lot of functions in humans' body as it is a cofactor for more than 300 enzymes. [125]. Besides, the anti-oxidant and anti-inflammatory effects of Zn, this element has vital roles in both innate and adaptive immune cells and also is essential for activation and secretion of insulin [126–128]. There are evidences of its protective effects against DM [129, 130].

Since zinc depletion deteriorates antiviral immunity, it is hypothesized that Zn deficiency may increase host susceptibility to COVID-19 [131].

Despite the lack of clinical data, some indications suggest that normal zinc status may be beneficial in COVID-19. According to the in vitro studies, zinc has antiviral activity through inhibition of a number of RNA polymerases [37]. Velthuis et al. indicated that the increased level of intracellular zinc can effectively inhibit the replication of SARS-CoV in cell culture [38]. It was also reported that papain-like protein 2, a viral protease of SARS-CoV that is fundamental for its virulence, is potently inhibited by zinc [132]. This antiviral actions of zinc against SARS-CoV may also apply to SARS-CoV2, since their genome have some similarity. Recently, Shittu et al., demonstrated the improving efficacy of

Chloroquine and Hydroxychloroquine against SARS-CoV-2 during combination with zinc supplementation [133]. Zinc may also have a modulatory effect on ACE2 activity, as the main receptor of SARS-CoV-2. Speth et al., showed that zinc exposure (100  $\mu$ M) reduced recombinant human ACE-2 activity in rat lungs [134].

Generally, according to the indirect evidences, Zn supplementation has a potential to decrease the incidence and also severity of SARS-CoV-2 infection, especially in groups with high risk of zinc deficiency including patients with DM, children and older adults [135].

## Conclusions

Nutritional deficiencies of protein, essential fatty acids and some micronutrients are associated with decreased immune function and increased susceptibility to viral infections including the novel coronavirus which can affect severity of infection especially in vulnerable patients like diabetics. Therefore, considering nutritional status of patients and appropriate macronutrient and adequate micronutrients intake is very important in the management of COVID-19.

There are some promising reports of the effectiveness of adequate protein, essential fatty acids and some micronutrients especially vitamins D, C, B12, folate and zinc and selenium on the prevention and treatment COVID-19. According to some recent researches reasonable supplementation of those nutrients can ameliorate the symptoms of COVID-19 through modulation of innate and adaptive immune responses and also direct effects on virus enzymes or its entrance to the host cells. However, further well-designed clinical trials are needed to determine their treatment dose.

**Abbreviations** 25(OH) D, 25-hydroxyvitamin D; 3CLpro, 3 C-Like protease; ACE2, Angiotensin-converting enzyme-2; AGEs, Glycosylation end products; ARDS, Acute respiratory distress syndrome; ASPEN, American Society for Parenteral and Enteral Nutrition; CD4+, cluster of differentiation 4+; CD8+, cluster of differentiation 8+; DCs, Dendritic cells; DM, Diabetes mellitus; DHA, Docosahexaenoic acid; EN, Enteral nutrition; EPA, Eicosapentaenoic acid; H1N1, a subtype of Influenza A virus; HBV, High biological value; MERS, Middle East respiratory syndrome; NK cells, Natural killer cells; nsp12, non-structural proteins 12; PN, Parenteral nutrition; RdRP, RNA-dependent-RNA polymerase; ROS, Reactive oxygen species; SARS-COV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; Se, Selenium; SOD, Superoxide dismutase; Th1, T Helper Cell Type 1; Th17, T Helper Cell Type 1; VitB12, Vitamin B12; VitC, Vitamin C; VitD, vitamin D; WHC, World Health Organization; Zn, Zinc

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**Data availability** No datasets were generated or analyzed during the current study.

## Declarations

**Ethics approval and consent to participate** It is not applicable.

**Consent for publication** It is not applicable.

**Conflict of interest** The authors declare that they have no competing interests.

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