The impact of vitamin and mineral supplements usage prior to COVID-19 infection on disease severity and hospitalization

Refat M. Nimer*, Omar F. Khabour, Samer F. Swedan, Hassan M. Kofahi

ABSTRACT

The COVID-19 pandemic has caused a global public health emergency. Nutritional status is suggested to be related to the severity of COVID-19 infection. Herein, we aimed to explore the impact of using vitamin and mineral supplements prior to COVID-19 infection on disease severity and hospitalization. In addition, the prior use of aspirin as an anticoagulant on the disease severity was investigated. A cross-sectional, self-administered survey was conducted between March and July 2021. Recovered COVID-19 individuals (age ≥ 18 years, n = 2148) were recruited in the study. A multivariate logistic regression was used to evaluate the associations of supplements and aspirin use with COVID-19 disease severity and hospitalization status. Among the participants, 12.1% reported symptoms consistent with severe COVID-19, and 10.2% were hospitalized due to COVID-19. After adjustment for confounding variables (age, gender, BMI, cigarette smoking status, and the number of comorbidities), the multivariate logistic regression model showed that the consumption of vitamin D supplements prior to COVID-19 infection was associated with a significant decrease in disease severity (OR = 0.68, 95% CI 0.50-0.92; p = 0.01), and a lower risk of hospitalization (OR = 0.64, 95% CI 0.45-0.89; p = 0.01). On the other hand, there were no significant differences in the frequencies of severe illness and hospitalizations with the consumption of vitamin A, folate acid, vitamin B12, vitamin B complex, vitamin C, zinc, iron, selenium, calcium, magnesium, omega 3, and aspirin before COVID-19 infection. Among the investigated nutrients, the use of vitamin D prior to COVID-19 infection was associated with reduced disease severity and hospitalization. However, more studies are required to confirm this finding.

KEYWORDS: COVID-19; supplements; vitamin D; hospitalization; severity

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a worldwide pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. According to the WHO, a total of 271,963,258 COVID-19 cases and 5,331,019 deaths were reported as of December 17th, 2021 [3]. SARS-CoV-2 infection is associated with a broad spectrum of symptoms ranging from moderate to severe pneumonia, coagulopathy, and death [4]. The percentage of severe cases requiring hospitalization varies from country to country but is estimated to account for 10-20% of all SARS-CoV-2 infections globally [5,6].

Dietary immunomodulators are substances that affect the functions of the immune system. Examples include vitamins A, C, D, E, and beta-carotene, as well as microelements such as zinc, selenium, and omega-3 fatty acids [7,8]. These substances are essential for acquired and innate immunity mediated by neutrophils, macrophages, natural killer cells, and T lymphocytes [7,9,10]. Therefore, deficiency in dietary immunomodulators could increase the risk of severe COVID-19 infection [11]. Such deficiencies can be corrected by following a healthy diet combined with the proper use of supplements. Although the use of vitamin and mineral supplements does not prevent infection with COVID-19 [12], it can improve immune status and subsequent disease severity [13,14]. Hence, the use of supplements has increased drastically during the COVID-19 pandemic [15].

Since COVID-19 has been shown to cause blood clotting, the use of aspirin has increased during the pandemic to overcome such complications. In addition to preventing clotting, aspirin reduces blood levels of interleukin-6 (IL-6), C-reactive protein, and macrophage colony-stimulating factor [16]. Therefore, aspirin use may help in reducing the occurrence of COVID-19-induced thrombosis and cytokine storm [17].

Several studies have reported the benefits of using vitamin and mineral supplements following a diagnosis of COVID-19 to improve the clinical course of the disease [18-21].
However, the benefits of regular intake of supplements before COVID-19 infection on the clinical course remain undefined. The study aimed to investigate the effect of regular use of supplements and aspirin before COVID-19 infection on disease severity and hospitalization status. We hypothesize that using some of these dietary supplements would be associated with reduced disease severity and fewer hospitalizations.

MATERIALS AND METHODS

Study design and participants

This study is part of the Jordanian COVID-19 survey project (JCSP). Ethical approval for the project was obtained from the institutional review board of Jordan University of Science and Technology (Ref.: 3/139/2021, dated: 30/03/2021). This cross-sectional study was conducted in Jordan between March and July 2021. The target population were individuals (≥18-years-old) who recovered from COVID-19 disease. The exclusion criteria included current COVID-19 infections and pre-infection vaccination status. Subjects who had been vaccinated prior to infection were excluded because vaccination strongly influences disease severity and thus may obliter ate any effect that could be observed when supplementation was used.

The study instrument

The study utilized a self-administered questionnaire in the Arabic language. The questionnaire collected information from participants on their demographics (such as age, gender, body mass index [BMI], and education), comorbidities, consumption of supplements (vitamins and minerals), and aspirin use prior to infection. In addition, information about disease symptoms and hospitalization status was collected. The questionnaire was face validated by a group of experts in the field and was piloted on a small sample of the population. Comments were obtained from experts and participants and were used to review and improve the clarity of the questionnaire. Data from the pilot study were not included in the final analyses.

Sampling procedure

The study followed a convenient sampling procedure. The questionnaire was prepared and administered using Google forms. To ensure anonymity, identifying information such as participants’ names and places of work were not collected. The first part of the questionnaire obtained informed consent and confirmed recovery from COVID-19. To ensure that the Jordanian population is well represented, trained research assistants recruited participants from different Jordanian governorates and assisted the participants in filling out the questionnaire. A total of 2148 participants completed the questionnaire.

COVID-19 severity classification

Disease symptoms were utilized to classify COVID-19 into two categories as previously reported [22]: severe and non-severe (asymptomatic, mild symptoms, and moderate). Mild cases included fever, sore throat, malaise, body pains, nausea, and other symptoms, but no signs or symptoms of pneumonia. Moderate cases included pneumonia (persistent fever and cough) but no hypoxemia (SpO$_2$ ≤ 92%). Severe cases were assigned to those with verified severe pneumonia and hypoxemia [22]. It is worth noting that some severe cases were not admitted to hospitals, which may be due to hospital overcrowding during the peak waves of the COVID-19. Therefore, such cases obtained medical care at home via private doctor visits, and some used medical oxygen supply systems at their homes.

Statistical analysis

The independent variables in the study were the use of supplements and aspirin. The dependent variables were COVID-19 severity and hospitalization. Frequencies and percentages were used for categorical variables. Means and standard deviations (SD) were used for continuous variables. The Chi-square was used to test differences in the severity/hospitalization between supplement/aspirin usage groups. Multivariate logistic regression analysis was used to explore the effect of supplement/aspirin usage on the severity/hospitalization after adjustment for possible confounders (age, gender, BMI, cigarette smoking, and number of comorbidities). The adjusted odds ratios (OR) and 95% confidence intervals (CI) were reported for each independent variable. A $p < 0.05$ was considered significant.

The data were analyzed using the Statistical Package for the Social Sciences version 23 (IBM Inc., Armonk, New York, United States).

RESULTS

Characteristics of study participants

Overall, 2148 individuals participated in the study. Table 1 summarizes participants’ characteristics. Females represented 58.2% of the study population. The mean age ± SD of the participants was 40 ± 16 years. Among the participants, 12.1% reported symptoms consistent with severe COVID-19. 10.2% were admitted to the hospital due to COVID-19. 23.1% had at least one comorbidity, and 16.9% were current cigarette smokers (Table 1).
Association of supplements and aspirin use with COVID-19 severity and hospitalization

The effects of supplements or aspirin use on the frequencies of COVID-19 severe cases and hospitalizations were investigated (Table 2). Among the supplements included in our study, consumption of vitamin D prior to COVID-19 infection was significantly associated with decreased frequencies of severe illness ($p = 0.04$) and hospitalization ($p = 0.03$). In addition, the rate of hospitalization was significantly decreased among the participants who consumed vitamin C before COVID-19 infection ($p = 0.03$). Vitamin C consumption was also associated with reduced disease severity. However, the difference did not reach statistical significance ($p = 0.07$). Moreover, a significantly higher frequency of severe illness and/or hospitalization was observed among participants who consumed selenium, omega 3, vitamin B complex, calcium, and magnesium supplements, and aspirin before COVID-19 infection (Table 2). On the other hand, there were no significant differences in the frequencies of severe illness and hospitalizations with the consumption of vitamin A, folic acid, vitamin B12, multivitamins, zinc, and iron before COVID-19 infection.

Logistic regression analyses

Next, to verify the associations above, we performed multivariate logistic regression analyses to control for the possible confounders such as age, gender, BMI, cigarette smoking, and the number of comorbidities. The ORs and 95% CI for the two outcomes, COVID-19 severity, and hospitalization status with the use of each supplement/aspirin, are presented in Table 3. The results of this model demonstrated that after adjusting for the confounders, vitamin D consumption was the only predictive factor to associate with lower risk of COVID-19 severity (OR = 0.68, 95% CI 0.50-0.92; $p = 0.01$, Table 3), and lower percentage of hospitalizations (OR = 0.63, 95% CI 0.45-0.89; $p = 0.01$, Table 3).

DISCUSSION

In this study, we investigated the impact of using vitamin and mineral supplements and aspirin prior to infection with COVID-19 on disease severity and hospitalization. Previous studies and clinical trials have focused on the impact of using vitamins and minerals during the infection on COVID-19 outcomes [14,23,24]. These studies reported significant effects of several vitamins and trace elements on reducing disease severity [25-27]. However, using these supplements prior to COVID-19 infection can give a powerful boost to the immune system. This increases its effectiveness in the early stages of the disease and could be crucial in determining disease outcome.

In a large survey of 349,598 participants in the UK, vitamin D levels were negatively associated with the probability of COVID-19 infection. After adjusting for confounders in multivariable analyses, this connection was not maintained [28]. In contrast, a large cohort study ($n = 108,343$) in Spain showed that people with serum vitamin D levels ≥ 30 ng/mL were more likely to have better COVID-19 outcomes after adjusting for outcome variables [29]. In our study, univariate analysis indicated associations between vitamin D and vitamin C consumption and reduced disease COVID-19 severity and hospitalization. However, using regression analysis to adjust for possible confounding factors, only vitamin D consumption was predicted to decrease the risk of severe disease and hospitalization. This indicates that confounding factors likely affected the observed association for vitamin C. Hemilä et al. reported that routine vitamin C supplementation is not justified and fails to reduce the incidence of colds and other respiratory infections [30]. Our findings are consistent with Demir et al., who showed that high vitamin D levels might reduce COVID-19 hospital stay and disease severity [31]. Lower vitamin D levels in COVID-19 patients compared to uninfected individuals were reported previously, suggesting a link between inadequate vitamin D levels and susceptibility to infection [32,33]. In addition, increased infection, hospitalization, and death from COVID-19 have been associated with low vitamin D levels [34-36]. Vitamin D has also been shown to increase the production of anti-inflammatory cytokines, such as IL-10, which is predicted to lower the severity of COVID-19 [37], and improve the activity of macrophages and T lymphocytes [38].

With the exception of vitamin D, adequate amounts of vitamins are obtained through the diet in most individuals [39,40]. However, according to US National Health and Nutrition Examination Survey (NHANES), about half of the respondents ($n = 6,261$) did not get sufficient vitamin D from food alone, including fortified products [41]. In addition, individuals with darker skin produce less vitamin D than those with lighter skin upon sun exposure [42]. Thus, vitamin D...
supplementation is necessary for maintaining optimal vitamin D levels. In agreement with our results, a meta-analysis of 25 studies with 11,321 participants in total found that vitamin D supplementation significantly reduced the risk of acute respiratory tract infections [43]. Furthermore, a meta-analysis conducted by Martineau et al. reported that vitamin D supplementation is associated with protection against acute respiratory infections [43]. Therefore, vitamin D supplementation is recommended during the infection with COVID-19, as well as before the infection as a preventative measure [44].

A significantly higher frequency of severe illness and hospitalization was observed among selenium users, omega 3, vitamin B complex, calcium and magnesium supplements, and aspirin. However, none of these supplements were predicted to increase the risk of severity/hospitalization in the logistic regression analyses. This discrepancy can be explained by regular usage of these supplements/aspirin is more frequent among individuals with a higher risk for severe illness such as the elderly and those with pre-existing medical conditions [45,46]. Therefore, controlling for these confounding factors is essential to demonstrate true associations between vitamins, minerals, and aspirin and either disease severity or hospitalization status.

Consistent with this conclusion, aspirin intake was not associated with COVID-19-related complications and mortality [47].

### TABLE 2. Severe COVID-19 and hospitalization cases according to use of supplements and substances prior to infection

| Supplement/substance taken before COVID-19 | Non-severe | Severe | p value | Hospitalized | | No | | Yes | p value |
|------------------------------------------|------------|--------|---------|--------------|--------|--------|--------|
| Vitamin C                                |            |        |         |              | 1330   | 88.8   | 167    | 11.2   | 0.03   |
| No                                       | 1303       | 87.0   | 194     | 13.0         | 0.07   |        |        |        |
| Yes                                      | 585        | 89.9   | 66      | 10.1         |        |        |        |        |
| Vitamin A                                |            |        |         |              | 1800   | 89.8   | 204    | 10.2   | 0.93   |
| No                                       | 1761       | 87.9   | 243     | 12.1         | 0.91   |        |        |        |
| Yes                                      | 127        | 88.2   | 17      | 11.8         |        |        |        |        |
| Vitamin D                                |            |        |         |              | 129    | 89.6   | 15     | 10.4   |        |
| No                                       | 1173       | 86.8   | 179     | 13.2         | 0.04   |        |        |        |
| Yes                                      | 715        | 89.8   | 81      | 10.2         |        |        |        |        |
| Omega 3                                  |            |        |         |              | 1620   | 90.4   | 172    | 9.6    | 0.04   |
| No                                       | 1585       | 88.4   | 207     | 11.6         | 0.08   |        |        |        |
| Yes                                      | 303        | 85.1   | 53      | 14.9         |        |        |        |        |
| Folic acid                               |            |        |         |              | 1732   | 89.5   | 203    | 10.5   | 0.17   |
| No                                       | 1694       | 87.5   | 241     | 12.5         | 0.13   |        |        |        |
| Yes                                      | 194        | 91.1   | 19      | 8.9          |        |        |        |        |
| Multivitamins                            |            |        |         |              | 1545   | 89.8   | 175    | 10.2   | 0.95   |
| No                                       | 1507       | 87.6   | 213     | 12.4         | 0.43   |        |        |        |
| Yes                                      | 381        | 89.0   | 47      | 11.0         |        |        |        |        |
| B complex vitamins                       |            |        |         |              | 1569   | 89.5   | 184    | 10.5   | 0.33   |
| No                                       | 1729       | 88.3   | 229     | 11.7         | 0.06   |        |        |        |
| Yes                                      | 159        | 83.7   | 31      | 16.3         |        |        |        |        |
| Vitamin B12                              |            |        |         |              | 161    | 84.7   | 29     | 15.3   |        |
| No                                       | 1533       | 87.5   | 220     | 12.5         | 0.18   |        |        |        |
| Yes                                      | 355        | 89.9   | 40      | 10.1         |        |        |        |        |
| Zinc                                     |            |        |         |              | 1644   | 90.2   | 178    | 9.8    | 0.12   |
| No                                       | 1608       | 88.3   | 214     | 11.7         | 0.23   |        |        |        |
| Yes                                      | 280        | 85.9   | 46      | 14.1         |        |        |        |        |
| Calcium                                  |            |        |         |              | 1720   | 90.4   | 183    | 9.6    | 0.01   |
| No                                       | 1680       | 88.3   | 223     | 11.7         | 0.13   |        |        |        |
| Yes                                      | 208        | 84.9   | 37      | 15.1         |        |        |        |        |
| Magnesium                                |            |        |         |              | 1810   | 90.3   | 195    | 9.7    | 0.01   |
| No                                       | 1769       | 88.2   | 236     | 11.8         | 0.08   |        |        |        |
| Yes                                      | 119        | 83.2   | 24      | 16.8         |        |        |        |        |
| Iron                                     |            |        |         |              | 1593   | 89.6   | 184    | 10.4   | 0.39   |
| No                                       | 1557       | 87.6   | 220     | 12.4         | 0.39   |        |        |        |
| Yes                                      | 331        | 89.2   | 40      | 10.8         |        |        |        |        |
| Selenium                                 |            |        |         |              | 1884   | 90.1   | 207    | 9.9    | 0.01   |
| No                                       | 1843       | 88.1   | 248     | 11.9         | 0.04   |        |        |        |
| Yes                                      | 45         | 78.9   | 12      | 21.1         |        |        |        |        |
| Aspirin                                  |            |        |         |              | 1585   | 92.1   | 136    | 7.9    | 0.00   |
| No                                       | 1559       | 90.6   | 162     | 9.4          | 0.00   |        |        |        |
| Yes                                      | 329        | 77.0   | 98      | 23.0         |        |        |        |        |

Refat Nimer, et al.: Dietary supplements and COVID-19
Currently, there is no direct evidence to indicate that omega-3 helps in the defense against COVID-19 [48].

Furthermore, logistic regression analysis indicated no association between B vitamins, calcium, and magnesium intake and COVID-19 severity. It is known that B vitamins regulate chemokine and cytokine production and mediate the interplay between immune cells involved in pathological processes [49]. However, the role of B vitamins in reducing COVID-19 severity is highly controversial [50, 51]. Similarly, the role of calcium and magnesium body status in COVID-19 manifestations is still controversial [52-54]. It is important to note that the use of supplements such as selenium, vitamin A, and folic acid was too low among the study participants. Therefore, more studies are needed to confirm the present findings.

Although this study assessed the impact of using aspirin and supplements prior to COVID-19 infection on disease severity and hospitalization based on a relatively large sample, it had some limitations. This was a cross-sectional study conducted using an anonymous questionnaire. The findings given were largely self-reported and were dependent on the participants’ reliability, honesty, and recallability. It is likely that some participants answered the questions in a way that they believed was objectively appropriate and not entirely correct. Some participants gave extreme responses based on their personal beliefs introducing some response biases.

Previous literature has shown that the severity of COVID-19 is elevated among the elderly, malnourished individuals, and those with high BMI or comorbidities [55-57]. Therefore, a regression analysis was applied to control for potential confounding factors in the current study. However, it is recommended that the relationship between supplement use and severity be examined in each subgroup with adequate samples in future studies. Among the limitations of the current investigation is that the study did not collect information regarding duration of illness and time of hospitalization. Therefore, the study could not examine the effect of supplement use on such measures. This could be the subject of future investigations. Furthermore, each participant’s rate of supplementary support during the infection was not equal. Furthermore, the levels of supplements and minerals used by the patients were unknown. Finally, since the study is questionnaire-based, fatal cases (that represent the highest severity) could not be included. Thus, more clinical studies are needed to confirm the present findings we are proposing within this study.

CONCLUSION

Our findings showed that vitamin D supplementation has protective effects against the severity and hospitalization of COVID-19 infection. Therefore, during this pandemic, persons at increased risk of vitamin D insufficiency should consider taking vitamin D supplements to maintain circulating vitamin D at an optimum range.

ACKNOWLEDGMENTS

The authors would like to acknowledge the deanship of the Research at Jordan University of Science and Technology for funding this project (grant number 20210173).

REFERENCES

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727-33. https://doi.org/10.1056/NEJMoa2001017

[2] Phelan AL, Katz R, Gostin LO. The novel Coronavirus originating in Wuhan, China: Challenges for global health governance. JAMA 2020;323(8):709-10. https://doi.org/10.1001/jama.2020.1097

[3] WHO. WHO Coronavirus (COVID-19) Dashboard 2021. Geneva: WHO. 2021. Available from: https://covid19.who.int

TABLE 3. Logistic regression analyses for supplements and aspirin use with COVID-19 severity and hospitalization as the output

| Supplement/substance taken before COVID-19 | Total number of users | Severity | Hospitalization |
|------------------------------------------|-----------------------|----------|-----------------|
|                                         | ρ | OR | 95% CI | ρ | OR | 95% CI |
| Vitamin C | 651 | 0.18 | 0.81 | 0.59-1.11 | 0.08 | 0.73 | 0.51-1.04 |
| Vitamin A | 144 | 0.36 | 0.77 | 0.43-1.36 | 0.40 | 0.77 | 0.42-1.41 |
| Vitamin D | 796 | 0.03** | 0.68 | 0.50-0.92 | 0.001** | 0.64 | 0.45-0.89 |
| Omega 3 | 356 | 0.43 | 1.15 | 0.81-1.65 | 0.30 | 1.23 | 0.83-1.80 |
| Folic acid | 212 | 0.16 | 0.69 | 0.40-1.17 | 0.23 | 0.70 | 0.39-1.26 |
| Vitamin B complex | 190 | 0.69 | 1.10 | 0.70-1.74 | 0.40 | 1.23 | 0.76-2.00 |
| Vitamin B12 | 395 | 0.06 | 0.70 | 0.48-1.02 | 0.15 | 0.74 | 0.49-1.11 |
| Zinc | 326 | 0.46 | 1.15 | 0.79-1.68 | 0.21 | 1.29 | 0.86-1.93 |
| Calcium | 245 | 0.76 | 0.94 | 0.61-1.43 | 0.40 | 1.21 | 0.78-1.88 |
| Magnesium | 143 | 0.73 | 1.69 | 0.66-1.81 | 0.24 | 1.36 | 0.81-2.29 |
| Iron | 371 | 0.83 | 1.04 | 0.70-1.55 | 0.37 | 1.22 | 0.79-1.88 |
| Selenium | 57 | 0.80 | 1.10 | 0.54-2.26 | 0.48 | 1.30 | 0.62-2.71 |
| Aspirin | 427 | 0.28 | 1.20 | 0.86-1.66 | 0.08 | 0.96 | 0.67-1.37 |

Each independent variable was adjusted for age, gender, BMI, cigarette smoking status, and the number of comorbidities. * * p ≤0.01; * p ≤0.05.
[4] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of Coronavirus disease 2019 (COVID-19): A review. JAMA 2020;324(8):782-93.

[5] Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of Coronavirus disease 2019: A model-based analysis. Lancet Infect Dis 2020;20(6):669-77. https://doi.org/10.1016/S1473-3099(20)30423-7

[6] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with COVID-19 using the ISARICO WHO clinical characterisation protocol: Prospective observational cohort study. BMJ 2020;369:m1985. https://doi.org/10.1136/bmj.m1985

[7] Polak E, Stepniewsk AE, Gol O, Tabakiewicz J. Potential immunomodulatory effects from consumption of nutrients in whole foods and supplements on the frequency and course of infection: Preliminary results. Nutrients 2021;13(1):1157. https://doi.org/10.3390/nu13011157

[8] Bae M, Kim H. The role of Vitamin C, Vitamin D, and selenium in immune system against COVID-19. Molecules 2020;25(22):51346.

[9] Xia X, Zhang X, Liu M, Duan M, Zhang S, Wei X, et al. Toward improved human health: Efficacy of dietary selenium on immunity at the cellular level. Food Funct 2021;12(3):976-84. https://doi.org/10.1039/d0fo03067h

[10] Arthur JR, McKenzie RC, Beckett GJ. Selenium in the immune system. J Nutr 2003;133 Suppl 5:1574-9S. https://doi.org/10.1093/jn/133.5.1457S

[11] Im JH, Je YS, Bae J, Chung MH, Kwon HY, Lee JS. Nutritional status of patients with COVID-19. Int J Infect Dis 2020;90:390-3. https://doi.org/10.1016/j.ijid.2020.05.018

[12] Speakman LL, Michienzi SM, Badowski ME. Vitamins, supplements and COVID-19: A review of currently available evidence. Drugs Context 2021;10:2021-6-2. https://doi.org/10.7573/dic.2021-6-2

[13] Kumar P, Kumar M, Bedi O, Gupta M, Kumar S, Jaiswal G, et al. Vitamin D deficiency is associated with COVID-19 severity: A protocol for systematic review and meta-analysis. Clin Epidemiol Glob Health 2021;12:100883. https://doi.org/10.1016/j.cleg.2021.100883

[14] Parasher A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgrad Med J 2021;97(1147):312-20. https://doi.org/10.1136/postgradmedj-2020-138577

[15] Güven M, Güleke H. The effect of high-dose parenteral Vitamin D on COVID-19-related clinical hospital mortality in critical COVID-19 patients during intensive care unit admission: An observational cohort study. Eur J Clin Nutr 2021;75(8):1138-8. https://doi.org/10.1038/s41430-021-00984-5

[16] Al Sulaiman K, Aljihani O, Saleh KB, Badreddin HA, Al Harthi A, Akenazi M, et al. Ascorbic acid as an adjunctive therapy in critically ill patients with COVID-19: A propensity score matched study. Sci Rep 2021;11(1):77048. https://doi.org/10.1038/s41598-021-96703-3

[17] Shakoor H, Feehan J, Mikkelsen K, Al Dhaheri AS, Ali HI, Platat C, et al. Confirmation of the high cumulative incidence of COVID-19. Maturitas 2020;133:Suppl 1:S207. https://doi.org/10.1016/j.maturitas.2020.08.007

[18] Klok FA, Kruip M, van der Meer NJ, Arbous MS, Gommers D, et al. Early nutritional interventions with Zinc, selenium and Vitamin D for raising anti-viral resistance against progressive COVID-19. Nutrients 2020;12(8):2358. https://doi.org/10.3390/nu12082358

[19] Kochi A, Tinkov A, Strand TA, Alhghani U, Saleh KB, Badreddin HA, Al Harthi A, Akenazi M, et al. Saxitoxin as an adjunctive therapy in critically ill patients with COVID-19. J Cell Physiol 2021;237(7):2098-9. https://doi.org/10.1002/jcp.29498

[20] Hacettepe CE, Mackay DE, Ho F, Celis-Morales CA, Kadikireddi SV, Niedzwiedz CL, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr 2020;14(4):5-15. https://doi.org/10.1016/j.dsx.2020.05.050

[21] Orestrell J, Oliva IC, Casado E, Subirana I, Dominguez D, Toloba A, et al. Vitamin D supplementation and COVID-19 risk: A population-based cohort study. J Endocrinol Invest 2022;45(1):167-75. https://doi.org/10.1530/JEO-21-01639-9

[22] Fernihough H, Chalker E, Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2004;4:CD000980. https://doi.org/10.1002/14651858

[23] Demir M, Demir E, Aygun H. Vitamin D deficiency is associated with COVID-19 positivity and severity of the disease. J Med Virol 2021;93(7):2992-9. https://doi.org/10.1002/jmv.26832

[24] Kaufman HW, Nichols IK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PLoS One 2020;15(9):e0239252. https://doi.org/10.1371/journal.pone.0239252

[25] Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D status and other clinical characteristics with COVID-19 test results. JAMA Netw Open 2020;3(9):e2019722. https://doi.org/10.1001/jamanetworkopen.2020.19722

[26] De Smet D, De Smet K, Vangeel P, Suskin I, Martens GA, et al. Vitamin D and COVID-19: A systematic review and meta-analysis. Front Immunol 2020;11:1712. https://doi.org/10.3389/fimmu.2020.01712
et al. Dietary reference intakes for Vitamin A, Vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. In: A Report of the Panel on Micronutrients. Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board Institute of Medicine. Washington, DC: National Academies Press; 2001.

[40] Palacios C, Gonzalez L. Is Vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol 2013;44 Pt A;138-45. https://doi.org/10.1366/j.sjbmb.2013.11.003

[41] Orces C, Lorenzo C, Guarneres JE. The prevalence and determinants of Vitamin D inadequacy among U.S. older adults: National health and nutrition examination survey 2007-2014. Cureus 2019;11(8):e5300. https://doi.org/10.7759/cureus.5300

[42] Springbett P, Buglass S, Young AR. Photoprotection and Vitamin D status. I Photochem Photobiol B 2010;102(1):160-8. https://doi.org/10.1016/j.ijbiophot.2010.03.006

[43] Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. BMJ 2017;356:j3568. https://doi.org/10.1136/bmj.j3568

[44] Abdulateef DS, Rahman HS, Salih JM, Osman SM, Mahmood TA, Omer SH, et al. COVID-19 severity in relation to sociodemographics and Vitamin D use. Open Med (Wars) 2021(16):591-609. https://doi.org/10.21051/med-2021-0073

[45] Bruyère O, Cavalier E, Souberbielle JC, Bischoff-Ferrari HA, Bergman P, et al. Vitamin D supplementation for preventing hip fracture among individuals aged 65 years and older. Cochrane Database Syst Rev 2014;7:CD005913. https://doi.org/10.1002/14651858.CD005913

[46] Zhao X, Zhang M, Li C, Ji Y, Zhang Y. Benefits of vitamins in the treatment of Parkinson's disease. Oxid Med Cell Longev 2019;2019:9426867. https://doi.org/10.1155/2019/9426867

[47] Son M, Noh MG, Lee JH, Seo J, Park H, Yang S. Effect of aspirin on Coronavirus disease 2019: A nationwide case-control study in South Korea. Medicine (Baltimore) 2021;100(30):e26670. https://doi.org/10.1097/MD.00000000000026670

[48] Dairwesh AM, Bassiouni W, Sosnowski DK, Seubert JM. Can N-3 polyunsaturated fatty acids be considered a potential adjuvant therapy for COVID-19-associated cardiovascular complications? Pharmacol Ther 2021;212:107703. https://doi.org/10.1016/j.pharmthera.2020.107703

[49] Huang S, Wei JC, Wu D, Huang Y. Vitamin B6 supplementation improves pro-inflammatory responses in patients with rheumatoid arthritis. Eur J Clin Nutr 2010;64(9):1007-13. https://doi.org/10.1038/ejcn.2010.107

[50] Tan CW, Ho LP, Kalimuddin S, Cheng BP, Teh YE, Thien SY, et al. Cohort study to evaluate the effect of Vitamin D, magnesium, and Vitamin B(12) in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition 2020;79-80:111017. https://doi.org/10.1016/j.nut.2020.111017

[51] Wei AK. COVID-19’s toll on the elderly and those with diabetes mellitus—is Vitamin B2 deficiency an accomplice? Med Hypotheses 2021;166:1010734. https://doi.org/10.1016/j.mehy.2020.103734

[52] Crespi B, Alcock J. Conflicts over calcium and the treatment of COVID-19. Evol Med Public Health 2021;11(1):149-56. https://doi.org/10.1093/emph/eoa2046

[53] Ebrahimzadeh-Attari V, Panahi G, Hebert JR, Ostadrahimi A, Saghafi-Asl M. Nutritional approach for increasing public health during pandem of COVID-19. A comprehensive review of antiviral nutrients and nutraceuticals. Health Promot Perspect 2021;11(2):119-36. https://doi.org/10.34172/hpp.2021.17

[54] Pinnawala NU, Thrastardottir TO, Constantinou C. Keeping a balance during the pandemic: A narrative review on the important role of micronutrients in preventing infection and reducing complications of COVID-19. Curr Nutr Rep 2021;10(3):200-10. https://doi.org/10.1007/s13668-021-00356-2

[55] Li Y, Zhu C, Zhang B, Liu L, Ji F, Zhao Y, et al. Nutritional status is closely related to the severity of COVID-19. A multi-center retrospective study. J Infect Dev Ctries 2021;15(4):490-500. https://doi.org/10.3855/jidc.14178

[56] Hussain A, Mahawar K, Xia Z, Yang W, EL-Hasani S. Obesity and Vitamin B12 deficiency as an accomplice? Med Hypotheses 2020;146:110374. https://doi.org/10.1016/j.mehy.2020.110374

[57] Lauc G, Sinclair D. Biomarkers of biological age as predictors of COVID-19 disease severity. Aging (Albany NY) 2020;12(8):6490-1. https://doi.org/10.18632/aging.103052