Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Short communication

Therapeutic and prognostic role of vitamin D for COVID-19 infection: A systematic review and meta-analysis of 43 observational studies

Fausto Petrelli a,*, Andrea Luciani a, Gianluca Perego b, Giuseppina Dognini c, Paolo Luigi Colombelli c, Antonio Ghidini d

a Oncology Unit, ASST Bergamo Ovest, Treviglio, BG, Italy
b Pharmacy Unit, San Raffaele Hospital, Milano, Italy
c Internal Medicine Unit, ASST Bergamo Ovest, Treviglio, BG, Italy
d Oncology Unit, Casa di cura Igea, Milano, Italy

ARTICLE INFO

Keywords:
COVID-19
Infection
Vitamin D3
Mortality
Meta-analysis

ABSTRACT

Vitamin D modulates the systemic inflammatory response through interaction with immune system. As such, it has a possible protective role against the risk of respiratory tract infections and other diseases. It may be useful in particular, during COVID-19 pandemic. PubMed, the Cochrane Library, and EMBASE were searched from inception until January 31, 2021, for observational or clinical studies reporting the prognosis (and therapeutic effect) of COVID-19 infection in patients with deficient vitamin D levels. The infection rate, severity, and death from COVID-19 infection were pooled to provide an odds ratio with a 95 % confidence interval (OR 95 % CI). An OR > 1 was associated with the worst outcome in deficient compared with nondeficient patients.

We assessed the association between vitamin D and risk, severity, and mortality for COVID-19 infection, through a review of 43 observational studies. Among subjects with deficient vitamin D values, risk of COVID-19 infection was higher compared to those with replete values (OR = 1.26; 95 % CI, 1.19–1.34; P < .01). Vitamin D deficiency was also associated with worse severity and higher mortality than in nondeficient patients (OR = 2.6; 95 % CI, 1.84–3.67; P < .01 and OR = 1.22; 95 % CI, 1.04–1.43; P < .01, respectively).

Reduced vitamin D values resulted in a higher infection risk, mortality and severity COVID-19 infection. Supplementation may be considered as preventive and therapeutic measure.

Vitamin D modulates the systemic inflammatory response through interaction with most cells of the immune system. As such, it has a possible protective role against the risk of respiratory tract infections and other diseases [1]. Vitamin D supplementation resulted in reduced all-cause mortality, according to a recently published meta-analysis [2].

We aimed to assess the association between vitamin D and risk, severity, and mortality for COVID-19 infection. PubMed, the Cochrane Library, and EMBASE were searched from inception until January 31, 2021, for observational or clinical studies reporting the prognosis (and therapeutic effect) of COVID-19 infection in patients with deficient vitamin D levels. The search terms were as follows: ((vitamin D [MeSH Terms]) or (vitamin D) or (25OH vitamin D) OR cholecalciferol OR ergocalciferol OR calcitriol) and (“covid-19”).

The infection rate, severity, and death from COVID-19 infection were pooled to provide an odds ratio with a 95 % confidence interval (OR 95 % CI). An OR > 1 was associated with the worst outcome in deficient compared with nondeficient patients.

The study adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. The study’s primary outcome was COVID-19 infection risk in vitamin D-deficient vs non-deficient patients. Secondary endpoints were severity (intensive care unit and/or mechanical ventilation), death, and therapeutic effect of vitamin D supplementation in COVID-19-affected patients.

The systematic search led to 43 eligible studies (Table 1) from 737 retrieved, mainly retrospective or observational studies (n = 612,601 patients), analyzing the effect of vitamin D deficiency or insufficiency and COVID-19 disease (infection, severity, or mortality). Among them, 8 reported on the therapeutic effect of supplementation on severity and mortality rate.

Among subjects with deficient vitamin D values, risk of COVID-19 infection was higher compared to those with replete values (OR = 1.26; 95 % CI, 1.19–1.34; P < .01). The funnel plot shows a minimal risk...
Table 1
Characteristics of included studies.

| Author/year       | Type of study       | N of pts | Vit. D3 cutoff (ng/mL) (%) | Median age (years) | Country | Infection risk in low vitamin D | Severity scale | Supplem. dose                                     | Type of analysis | NOS score |
|-------------------|---------------------|----------|---------------------------|-------------------|---------|---------------------------------|----------------|-----------------------------------------------|-----------------|----------|
| Abdollahi/2020    | Retrospective       | 402      | 30 (80.5)                 | 47.1              | Iran    | ↑                               | –              | –                                             | –               | 6        |
| Abrishami/2020     | Retrospective       | 73       | 25 (-)                    | 55.1              | Iran    | –                               | –              | –                                             | MVA             | 5        |
| Alguwaihes/2020   | Retrospective       | 439      | 20 (-)                    | 55                | Saudi Arabia | –                               | ICU            | –                                             | MVA             | 6        |
| Annweiler/2020    | Retrospective       | 77       | –                          | 88                | France  | –                               | –              | –                                             | –               | 5        |
| Annweiler/2020    | Retrospective       | 66       | –                          | 87.7              | France  | –                               | –              | –                                             | MVA             | 5        |
| Baktash/2020      | Prospective cohort  | 105      | 30 (55.7)                 | 81.3              | Cyprus  | –                               | NIV            | –                                             | –               | 6        |
| Barassi/2021      | Retrospective       | 118      | 20 (44.9)                 | 61                | Italy   | –                               | CPAP/NIMV      | –                                             | UVA             | 6        |
| Bennouar/2021     | Prospective         | 120      | 20 (55.9)                 | 62.3              | Algeria | –                               | –              | –                                             | MVA             | 6        |
| Blanch-Rubio/2020 | Cross-sectional     | 2102     | –                          | 66.4              | Spain   | –                               | –              | –                                             | –               | 7        |
| Cangiano/2020     | Observational       | 157      | –                          | 89.8              | Italy   | –                               | –              | –                                             | MVA             | 6        |
| Careda/2020       | Prospective cohort  | 129      | 20 (76.7)                 | 77                | Italy   | –                               | –              | MVA                                          | –               | 6        |
| Chang/2020        | Retrospective       | 992      | –                          | –                 | US      | ↑                               | –              | –                                             | –               | 8        |
| De Smet/2020      | Retrospective       | 186      | 20 (59)                   | 69                | Belgium | –                               | –              | –                                             | MVA             | 6        |
| Demir/2020        | Retrospective       | 487      | 30 (93)                   | 44.6              | Turkey  | ↑                               | –              | –                                             | UVA             | 6        |
| Entrenas Castillo/2020 | Randomized          | 76       | –                          | 52.9              | Spain   | –                               | –              | 0.532 mg d1, 0.266 mg d3,7 then weekly       | MVA             | 5        |
| Ferrari/2020      | Retrospective       | 347      | 30 (78.9)                 | 65                | Italy   | ↑                               | –              | –                                             | UVA             | 6        |
| Giannini/2021     | Retrospective       | 91       | 20 (-)                    | 74                | Italy   | ↑                               | –              | 200,000 IU in two consecutive days            | MVA             | 6        |
| Hastie/2020       | Retrospective       | 656      | 20 (-)                    | –                 | UK      | ↑                               | –              | 25,000 IU monthly or 5600 IU weekly           | UVA             | 6        |
| Hernandez/2020    | Case-control        | 403      | 20 (-)                    | 61                | Spain   | –                               | ICU            | –                                             | –               | 7        |
| Jain/2020         | Prospective         | 154      | 20 (58.4)                 | 46.8              | India   | –                               | ICU            | –                                             | –               | 6        |
| Karahan/2020      | Retrospective       | 149      | 30 (91.9)                 | 65                | Turkey  | –                               | –              | –                                             | MVA             | 6        |
| Katz/2021         | Retrospective       | 884      | –                          | –                 | US      | ↑                               | –              | –                                             | MVA             | 7        |
| Kaufman/2020      | Retrospective       | 191,779  | 20 (12.5)                 | 54                | US      | ↑                               | –              | –                                             | MVA             | 8        |
| Li/2021           | Prospective         | 353,299  | 25 (12.1)                 | 67.7              | UK      | ↑                               | –              | Not defined                                   | –               | 6        |
| Ling/2020         | Retrospective       | 444      | 25 (37.8)                 | 74                | UK      | ↑                               | –              | –                                             | Various doses    | 6        |
| Lohia/2021        | Retrospective       | 270      | 20 (35.2)                 | 63.81             | US      | ↑                               | –              | ICU                                          | MVA             | 6        |
| Luo/2020          | Retrospective       | 335      | 30 (65.1)                 | 56                | China   | ↑                               | –              | Various criteria                              | –               | 7        |
| Ma/2021           | Prospective         | 8297     | 20 (-)                    | 58.2              | UK      | ↓                               | –              | –                                             | MVA             | 6        |
| Macaya/2020       | Retrospective       | 80       | 20 (56)                   | –                 | Spain   | –                               | –              | Various criteria                              | –               | 6        |
| Maghbobi/2020     | Retrospective       | 325      | 30 (67.2)                 | 58.7              | Iran    | –                               | –              | Not defined                                   | –               | 6        |
| Mariani/2020      | Registry data       | 37,900   | 20 (49)                   | –                 | International | ↑                               | –              | –                                             | MVA             | 6        |
| Melitzer/2020     | Retrospective       | 489      | 20 (25)                   | 49.2              | US      | ↑                               | –              | –                                             | MVA             | 6        |
| Mendy/2020        | Retrospective       | 689      | 20 (12.9)                 | 49.5              | US      | ↑                               | ICU or death | –                                             | MVA             | 6        |
| Merzon/2020       | Population-based study | 7807   | 30 (13.4)                 | 35.5              | Israel  | ↑                               | –              | –                                             | MVA             | 6        |
| Pal/2020          | Retrospective       | 72       | 20 (97)                   | 36                | India   | ↑                               | –              | –                                             | UVA             | 6        |

(continued on next page)
of publication bias for the primary endpoint analysis (Egger test $P = .04$). Where deficient (<20 ng/mL) vitamin D cutoff was used, the risk of infection was 50% higher compared to subjects with nondeficient values (OR 1.5, 95% CI 1.08–2.08; $P = .02$). Vitamin D deficiency was also associated with worse severity and higher mortality than in non-deficient patients (OR 2.6; 95% CI, 1.84–3.67; $P < .01$, Fig. 1, and OR = 1.22; 95% CI, 1.04–1.43; $P < .01$, respectively).

In n = 6 and n = 7 studies respectively, supplementation with various vitamin D doses reduced the risk of severe forms and death events in COVID-19-infected patients (OR = 0.27; 95% CI, 0.11–0.66; $P < .01$ and OR = 0.41; 95% CI, 0.21–0.81; $P = .01$).

Vitamin D influences the expression of various genes involved in the immune system (innate immunity, adaptive immunity) and the downstream inflammatory cascade, thus affecting the susceptibility to and severity of bacterial and viral infections [3,4]. Supplementation with vitamin D may be useful in COVID-19 infection, as both a preventive and therapeutic agent [5]. Vitamin D deficiency correlates strongly with infection risk in observational studies, which is likely linked to the impaired immune response to viral infection. Older persons with a weaker immune system and associated comorbidities are more vulnerable to dysfunctional immune responses, as most of them concomitantly have severe hypovitaminosis D. Gene response analysis revealed that vitamin D binds with its receptor and may affect 2 different pathways: (i) It inhibits the expression of pro-inflammatory cytokines interfering with the TNF-induced NFkB1 signaling pathway, and (ii) it initiates the expression of interferon-stimulating genes devoted to antiviral response activating the IFN-$\alpha$-induced Jak-STAT signaling pathway [6]. This action mode explains why vitamin D deficiency is associated with mortality and severity of COVID-19 infection in our meta-analysis. In light of the present data and recent published health authorities’ recommendations, 7 check and supplementation with vitamin D of subjects with deficient levels should be a priority during the COVID-19 pandemic.

Authors statement

Fausto Petrelli: Conceptualization, Methodology, Software Writing-Original draft preparation.
Antonio Ghidini, Gianluca Perego: Data curation.
Andrea Luciani: Supervision, Visualization, Investigation.
Paolo Colombelli: Supervision.
Giuseppina Dognini: Writing- Reviewing and Editing.

Table 1 (continued)

| Author/year | Type of study | N of pts | Vit. D3 cutoff (ng/mL) | Median age (years) | Country | Infection risk in low vitamin D | Severity scale | Supplem.dose | Type of analysis | NOS score |
|-------------|---------------|----------|-----------------------|-------------------|---------|-------------------------------|----------------|-------------|----------------|-----------|
| Panagiotou/2020 | Retrospective | 124 | 20 (37.3) | 68.7 | UK | – | ICU | – | UVA | 6 |
| Radujkovic/2020 | Retrospective | 185 | 30 (22) | 60 | Germany | – | MV or death | – | MVA | 7 |
| Raisi-Estabhrah/2020 | Prospective | 1326 | – | 68.1 | UK | – | – | – | MVA | 6 |
| Szeto/2020 | Retrospective | 700 | 20 (37.6) | 63 | US | – | ICU or death | – | MVA | 6 |
| Tan/2020 | Prospective | 43 | – | 61.2 | Asia | – | – | – | 1000 IU die | MVA | 6 |
| Vessailio/2020 | Prospective | 30 | 15 (80) | 65 | Greece | – | – | – | UVA | 7 |
| Ye/2020 | Case-control | 142 | 20 (29) | 42.5 | China | † | Not defined | – | MVA | 6 |

* refers to COVID-19 infected patients.
† oral calcifediol; ICU, intensive care unit; NIV, non-invasive ventilation; NIMV, non-invasive mechanical ventilation; MV, mechanical ventilation; CPAP, continuous positive airway pressure; UVA, univariate analysis; MVA, multivariate analysis.

Fig. 1. Risk of covid-19 severity in patients with low vitamin D levels.
Funding

The authors declare no funding.

References

[1] A.K. Heath, I.Y. Kim, A.M. Hodge, D.R. English, D.C. Muller, Vitamin D status and mortality: a systematic review of observational studies, Int. J. Environ. Res. Public Health 16 (3) (2019) 383, https://doi.org/10.3390/ijerph16030383.

[2] Y. Zhang, F. Fang, J. Tang, L. Jia, Y. Feng, P. Xu, A. Faramand, Association between vitamin D supplementation and mortality: systematic review and meta-analysis, BMJ 366 (2019), 14673, https://doi.org/10.1136/bmj.l4673. Erratum in: BMJ. 2020;370:m2329.

[3] J.A. Kempker, G.S. Martin, Vitamin D and sepsis: from associations to causal connections, Inflamm. Allergy Drug Targets 12 (2013) 000.

[4] M.T. Zdrenghea, H. Makrinioti, C. Bagacean, et al., Vitamin D modulation of innate immune responses to respiratory viral infections, Rev. Med. Virol. 27 (2017) e1999.

[5] J. Arboleda, S. Urcuqui-Inchima, Vitamin D supplementation: a potential approach for COVID-19 therapeutics? Front. Immunol. (2020) 11.

[6] F. Ahmed, A network-based analysis reveals the mechanism underlying vitamin D in suppressing cytokine storm and virus in SARS-CoV-2 infection, Front. Immunol. 11 (2020), 590459, https://doi.org/10.3389/fimmu.2020.590459.