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Applied nutritional investigation

Vitamin D supplementation and outcomes in coronavirus disease 2019 (COVID-19) patients from the outbreak area of Lombardy, Italy

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Introduction

Recent literature has substantially raised interest in the immune-modulating properties of vitamin D against coronavirus disease 2019 (COVID-19). Although several viewpoints have been published, data supporting the hypothesized beneficial role are limited and controversial [1,2]. Consistent with a systematic review reporting the protective role of 25-hydroxyvitamin D (25OHD) supplementation [3], in a recent survey conducted in individuals with Parkinson disease (PD), those with COVID-19 were more likely not to be taking supplements than participants who were unaffected [4]. The observation of lower mortality rates at lower degrees of latitude, along with other preliminary reports on the association between serum levels of 25OHD and the risk of having the disease or a critical outcome, have suggested that vitamin D could modulate the risk and mitigate the severity of COVID-19 [1,2,5]. There is evidence that vitamin D has immunomodulatory functions and plays an antiinflammatory role, particularly in viral infections. It has also been demonstrated to be inversely correlated to acute respiratory distress syndrome and increased levels of C-reactive protein [6]. On the other hand, the higher prevalence of 25OHD deficiency in many disease conditions is questionable according to a reversed causality hypothesis, as the underlying disease and related inflammatory background may negatively influence 25OHD metabolism, particularly that of its binding protein, resulting in substantial bias in the assessment of its status [7,8]. This is also suggested by differences in serum levels between those who are positive and negative on polymerase chain reaction tests, which might not only be interpreted as a higher susceptibility to infection in those with deficiency status [5,9]. Therefore, we aimed to evaluate whether 25OHD supplementation, which may be a better surrogate of real 25OHD status, is associated with prognosis in COVID-19 patients from the Italian outbreak area of Lombardy.

Methods

The study was approved by local institutional ethics committees, and written informed consent was obtained from every participant.

Two sets of data collected prospectively during the outbreak of the pandemic in the north of Italy were pooled and analyzed. The first consisted of COVID-19 PD patients (group 1) and COVID-19 PD caregivers (group 2) identified from a pool of...
Vitamin D could boost mucosal defenses and protect against infections [1–6], and it has been suggested to down-regulate the inflammatory burden contributing to acute respiratory distress syndrome and lung injury [2,10,11], the main cause of death in COVID-19 patients. Enhanced ACE2 expression is considered a protective factor in acute lung injury [10,11]. Vitamin D increases the expression of ACE2 [6], and this may apply not only to airway epithelium but also to other organs and monocyte-derived macrophages. However, ACE2 is the binding site of SARS-CoV-2, and increased ACE2 expression may result in enhanced viral hemolysis and organ damage, as well as an aberrant innate immune response with hyperactivation of macrophages [11]—perhaps at least in patients with high complication, such as those admitted in our outbreak area.

Our data may appear in contrast with recent literature suggesting that higher serum 25OHD is associated with more favorable COVID-19 outcomes, with lower progression of respiratory illness and to critical illness, as well as lower mortality rates [1,2,5,12], although no association has been also reported [13]. However, disease-related inflammation may negatively affect 25OHD metabolism, particularly that of its binding protein, resulting in reduced circulating levels and assessment bias [7,8]. From this perspective, the timing of assessment in relation to the onset of symptoms could also play a role [13]. It is with this background that we decided to evaluate the association between supplementation rather than serum levels and outcome. Nonetheless, we evaluated serum 25OHD in a subgroup of consecutive patients, demonstrating that supplementation results in substantially higher and adequate circulating levels.

Therefore, although the potential utility of vitamin D in the prevention of respiratory-tract infections is more substantial [3], its benefits in COVID-19 (prevention and management) still need to be clarified by appropriate intervention trials.

We recognize the following limitations. First, a larger study population, along with multicenter participation, would have resulted in increased statistical power and bias reduction. However, we were not able to perform a valid calculation of the sample size, due to the emergency crisis and the heterogeneity in published data on outcomes and use of supplements. Indeed, we recognize that the emergency crisis was a source of bias itself, as it is likely that only individuals with the worst cases were hospitalized in our outbreak area. Finally, in agreement with Italian recommended dietary

### Table 1

| Characteristic                  | Group 1 (PD patients, n = 105) | Group 2 (caregivers of PD patients, n = 92) | Group 3 (hospital inpatients, n = 127) | Supplemented (n = 38) | Non-supplemented (n = 286) | P* |
|---------------------------------|--------------------------------|---------------------------------------------|----------------------------------------|-----------------------|---------------------------|----|
| Male sex, n (%)                 | 55 (52.4)                      | 44 (47.8)                                   | 58 (45.7)                              | 16 (42.1)             | 141 (49.3)                 | 0.49|
| Age, y, mean (SD)               | 70.5 (10.1)                    | 65.4 (11.0)                                 | 73.5 (14.7)                            | 68.8 (10.6)           | 70.5 (13.1)                | 0.39|
| Body mass index, kg/m², mean (SD)  | 25.6 (4.9)                     | 25.2 (4.4)                                  | 25.1 (4.5)                             | 25.1 (4.5)            | 25.4 (4.4)                 | 0.74|
| Obesity, n (%)                  | 19 (18.1)                      | 13 (14.1)                                   | 14 (11.0)                              | 5 (13.2)              | 41 (14.3)                  | 0.99|
| Comorbidities, n (SD)           | 1.6 (0.7)                      | 0.9 (0.8)                                   | 1.9 (1.3)                              | 1.5 (1.2)             | 1.5 (1.1)                  | 0.92|
| Ischemic heart disease, n (%)   | 5 (4.8)                        | 5 (5.4)                                     | 51 (40.2)                              | 8 (21.1)              | 53 (18.5)                  | 0.66|
| Hypertension, n (%)             | 44 (41.9)                      | 51 (55.4)                                   | 87 (68.5)                              | 20 (52.6)             | 162 (56.6)                 | 0.73|
| Diabetes, n (%)                 | 8 (7.6)                        | 11 (12.0)                                   | 38 (29.9)                              | 6 (15.8)              | 51 (17.8)                  | 1.00|
| COPD, n (%)                     | 6 (5.7)                        | 8 (8.7)                                     | 15 (11.8)                              | 2 (5.3)               | 27 (9.4)                   | 0.55|
| Cancer, n (%)                   | 1 (0.9)                        | 2 (2.2)                                     | 26 (20.5)                              | 6 (15.8)              | 20 (7.0)                   | 0.10|
| PD, n (%)                       | 105 (100)                      | 0 (0)                                       | 1 (0.1)                                | 13 (34.2)             | 93 (32.5)                  | 0.86|
| Vitamin D supplementation, n (%)| 13 (12.4)                      | 14 (15.2)                                   | 11 (8.7)                               | 32.9 (14.8)           | 11.3 (8.6)                 | <0.001|
| Serum 25OHD, ng/mL, mean (SD)*  | —                              | —                                           | 132.1 (11.1)                           | —                     | 132.9 (14.8)               | 11.3 (8.6) |
| Hospitalization, n (%)          | 18 (17.1)                      | 25 (27.2)                                   | —                                      | —                     | —                          | — |
| In-hospital mortality, n (%)    | 6 (33.3)                       | 7 (28.0)                                    | 34 (26.8)                              | —                     | —                          | — |

25OHD, 25-hydroxyvitamin D; COPD, chronic obstructive pulmonary disease; PD, Parkinson disease; SD, standard deviation.

*Supplemented versus non-supplemented according to the unpaired Student’s t test (continuous variables) or the Fisher’s exact test (categorical variables).

1Including PD.

2In hospital inpatients only.

3In-hospital mortality (%) has been calculated according to the number of hospitalized patients.
allowances [14], we decided to define supplementation as an intake of at least 25,000 IU/mo (~800 IU/d) in the previous 3 mo. It is not at all clear that supplements of <1000 IU/d are likely to make much difference compared with larger ones. However, the mean intake for participants taking supplements was >54,000 IU/mo (>1800 IU/d), resulting in adequate circulating levels in most participants.

In conclusion, 25OHD supplementation was not associated with hospitalization but appeared to be a risk factor for higher in-hospital mortality in COVID-19. Further studies are needed to clarify the role of vitamin D supplementation and status in modulating the severity of COVID-19, as well as preventing it.

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Table 2
Association between vitamin D supplementation and outcomes (logistic regression)

| Outcome                  | Case population, n | 25OHD supplemented | 25OHD non-supplemented | OR (95% CI)* P | Adjusted OR (95% CI)* P |
|--------------------------|--------------------|---------------------|------------------------|----------------|------------------------|
|                          | Patients, n Events, n (%) | Patients, n Events, n (%) |                         |                |                        |
| Hospitalization          | 197 27 7 (25.9)    | 170 36 (21.2)       | 1.30 (0.51–3.32) 0.56  | 1.25 (0.46–3.35) 0.66 |
| In-hospital mortality    | 170 18 7 (38.9)    | 152 40 (26.3)       | 1.78 (0.64–4.91) 0.26  | 2.42 (0.78–7.49) 0.13 |

25OHD, 25-hydroxyvitamin D; CI, confidence interval; OR, odds ratio; PD, Parkinson disease.
*ORs are provided for the supplemented group (reference category: non-supplemented group, OR = 1).

Adjusted for sex, body mass index, PD, and number of other comorbidities.

25OHD, 25-hydroxyvitamin D; CI, confidence interval; OR, odds ratio; PD, Parkinson disease.
*ORs are provided for the supplemented group (reference category: non-supplemented group, OR = 1).

Adjusted for sex, body mass index, PD, and other clinical characteristics.

25OHD, 25-hydroxyvitamin D; CI, confidence interval; OR, odds ratio; PD, Parkinson disease.
*ORs are provided for the supplemented group (reference category: non-supplemented group, OR = 1).

Adjusted for sex, body mass index, PD, and number of other comorbidities.