The role of vitamin D supplementation in COVID-19:
Intervention studies with cholecalciferol or with calcifediol

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1. Introduction

A vitamin D deficiency plays an important role in a severe course of COVID-19. On November 23, 2021, 47 peer-reviewed trials were known in which cholecalciferol or calcifediol was given in addition to usual medication for the treatment of vitamin D deficiency in COVID-19.[1]
In the body, the cholecalciferol obtained from sunlight or from supplements is converted by the liver into calcifediol.[2] This conversion depends on the dose administered and takes several weeks.[3] Using cholecalciferol, a sufficiently high vitamin D status can only be achieved within a few days when using a non-physiologically high suppltion dose.[4]

However, calcifediol can also be administered orally in capsule form, using capsules containing 0.266 mg calcifediol. In the Netherlands, these have been included in the Medicines Reimbursement System (GVS) under the brand name Hidroferol® since 1 July 2021, as described in Farmacotherapeutic Kompas for the treatment of a vitamin D deficiency. The advantage of this drug is the rapid absorption and increase of the vitamin D level in the blood within about 4 hours after administration. [5-7] Several intervention studies have used this agent.

The aim of this paper is to describe the results of available peer-reviewed intervention studies with cholecalciferol and calcifediol in COVID-19, and their effect on mortality probability and risk of possible ICU admission.

2. Methods

A large number of scientific studies into the effectiveness of vitamin D supplementation are available, some of which are peer-reviewed and some are not (yet) peer-reviewed.[1] The peer-reviewed studies can be found on Pubmed, a website that is used worldwide to access the peer-reviewed medical scientific literature.

Results can be categorized by time of treatment (early, late, prophylactic) and by drug used (cholecalciferol or calcifediol). The objective per study could also differ (risk of death and serious course). In addition, studies have been compared with regard to the chance of IC admission.

Differences in design of the studies also differed among themselves, as indicated:

RCT	randomized controlled trial
DB RCT	double blind randomized controlled trial
QR	quasi randomized

3. Results

In the peer-reviewed trials, a trend in favor of an increase in vitamin D status by treatment with cholecalciferol or calcifediol was found in 39 of these 47 studies, with a significant benefit for treatment in 18 of these intervention studies. While eight studies showed a trend in favor of vitamin D treatment, in all studies this adverse trend was non-significant, as shown in Table 1.[1]

3.1 Risk reduction for mortality and severity of the course with early and late treatment

Splitting in Table 1 into timely and late treatment showed that late treatment led to a significantly less favorable outcome compared to timely treatment. Here the relative risk (RR) is stated with the confidence interval [CI]:

- With early or timely treatment, a meta-analysis from four studies showed a significant benefit for treatment with vitamin D, with a risk reduction of 84% (RR 0.16 [0.08-0.32]). This mainly concerned the risk of death.
- With late treatment, 18 studies showed a much lower risk reduction of 54% (RR 0.46 [0.33 – 0.65]). Again, this mainly concerned the risk of death.

3.2 Risk reduction for mortality and severity of the course with late treatment with cholecalciferol or calcifediol

Studies using late treatment with cholecalciferol or with calcifediol are detailed separately in Tables 2 and 3. Most studies were peer-reviewed; only one small study from Table 2 was not peer-reviewed (Leal *et al*.).

The results showed a large difference between late treatment with cholecalciferol and calcifediol. With late treatment, calcifediol had a clear benefit, as shown in Table 2 and Table 3:

- A meta-analysis for the 14 studies for late treatment with cholecalciferol (including the small non-peer-reviewed study by Leal) showed a significant risk reduction (especially with regard to risk of death) of 45% (RR 0.55 [0.40 – 0.76]), as shown in Table 2.

- A meta-analysis for the five peer-reviewed studies using late treatment with calcifediol showed a significant risk reduction for the risk of death of 78% (RR 0.22 [0.15 – 0.33]), as shown in Table 3.

The result for late treatment with calcifediol is comparable to the result for early treatment with cholecalciferol as given in Table 1, which were all studies with cholecalciferol; these showed a risk reduction of 84% (RR 0.16 [0.08 - 0.32]).

Table 1. Peer-reviewed trials in vitamin D treatment. (Figure 9 from ref. [1]).
(All associated references are given in ref. [1]).

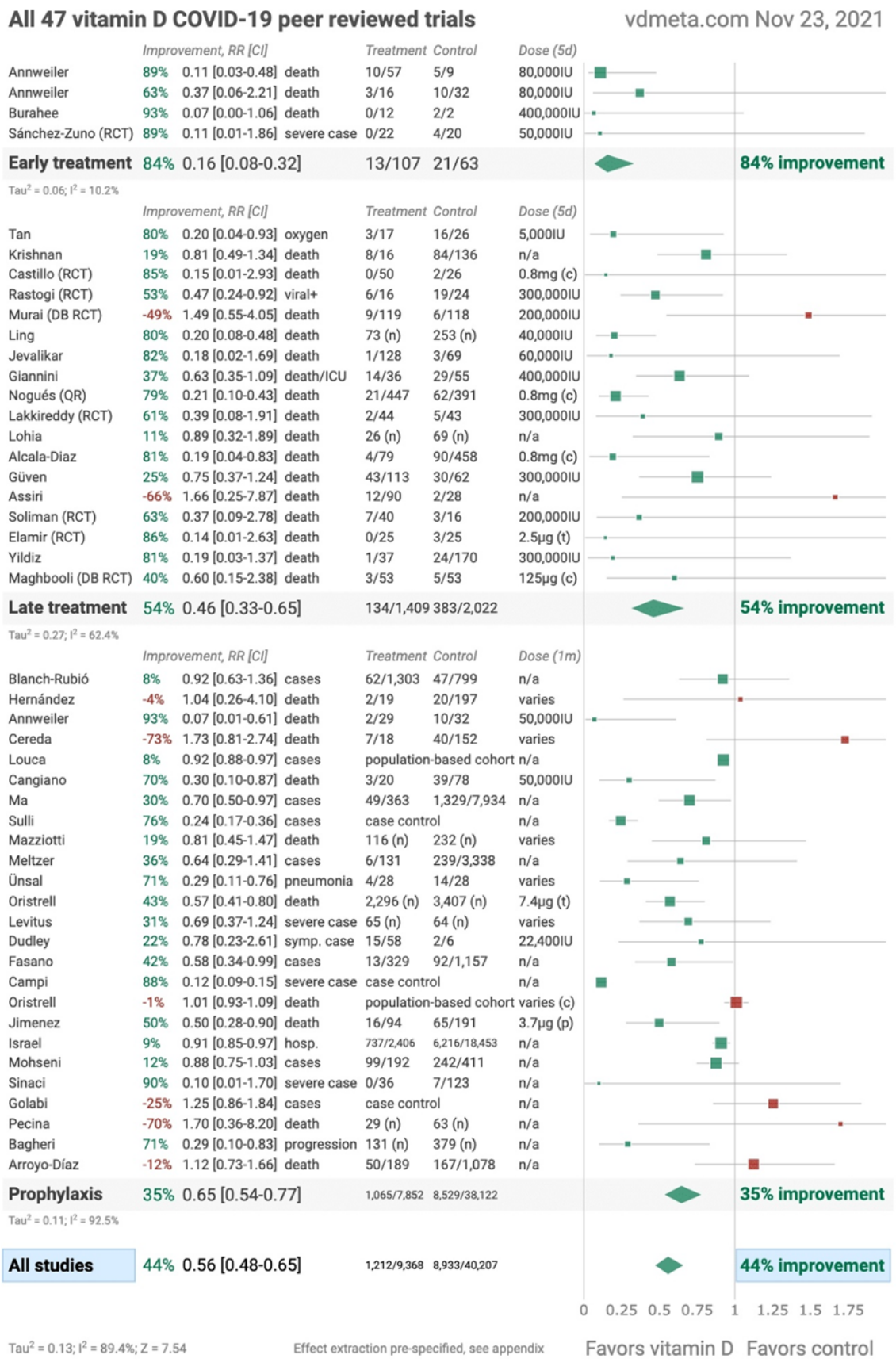


Table 2. Trials with late cholecalciferol treatment. (Part of Figure 10 from ref. [1]).
Note: the trial by Leal *et al*. was the only one not peer-reviewed.
(All associated references are given in ref.[1]).

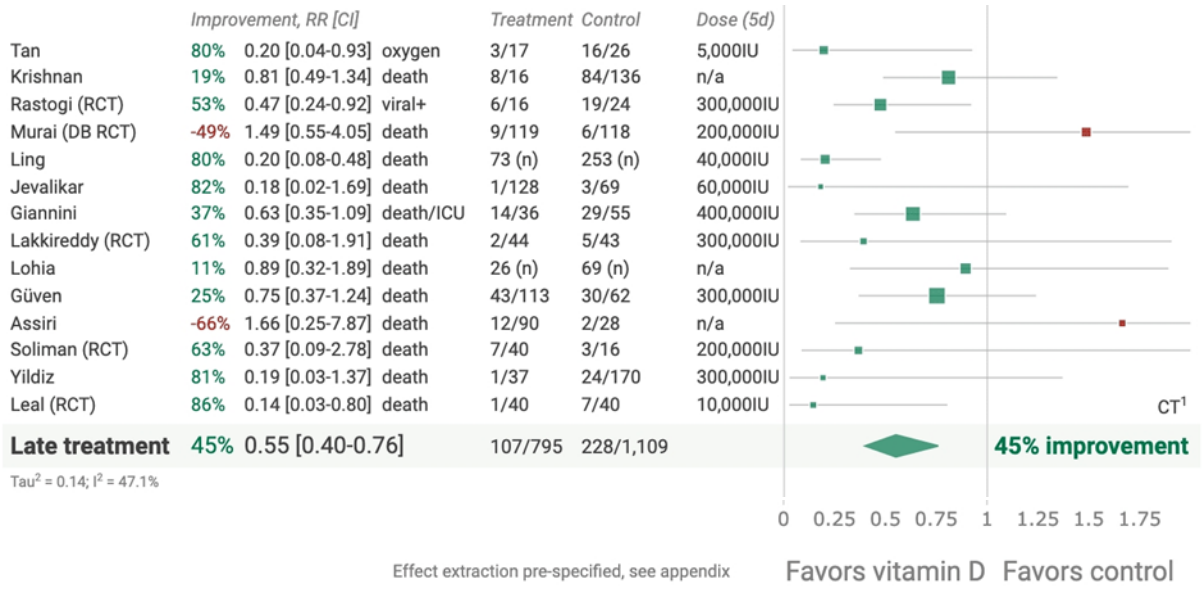
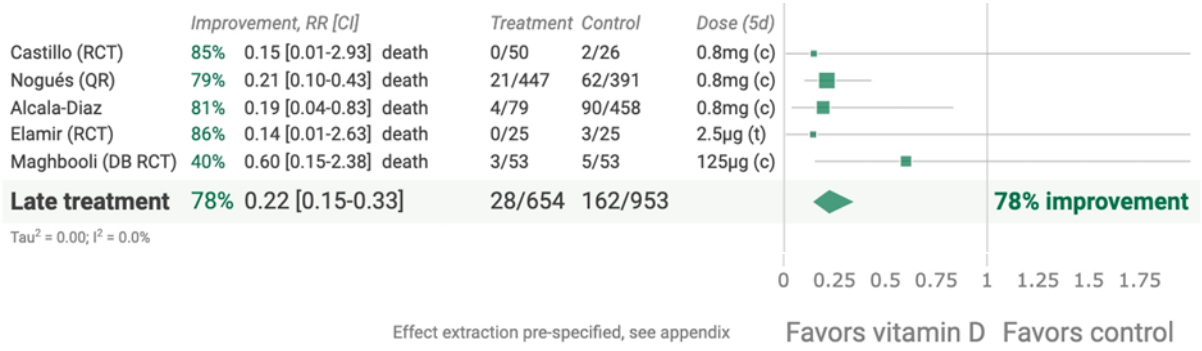


Table 3. Peer-reviewed trials in late calcifediol treatment (Figure 11 from ref. [1]).
(All associated references are given in ref.[1]).

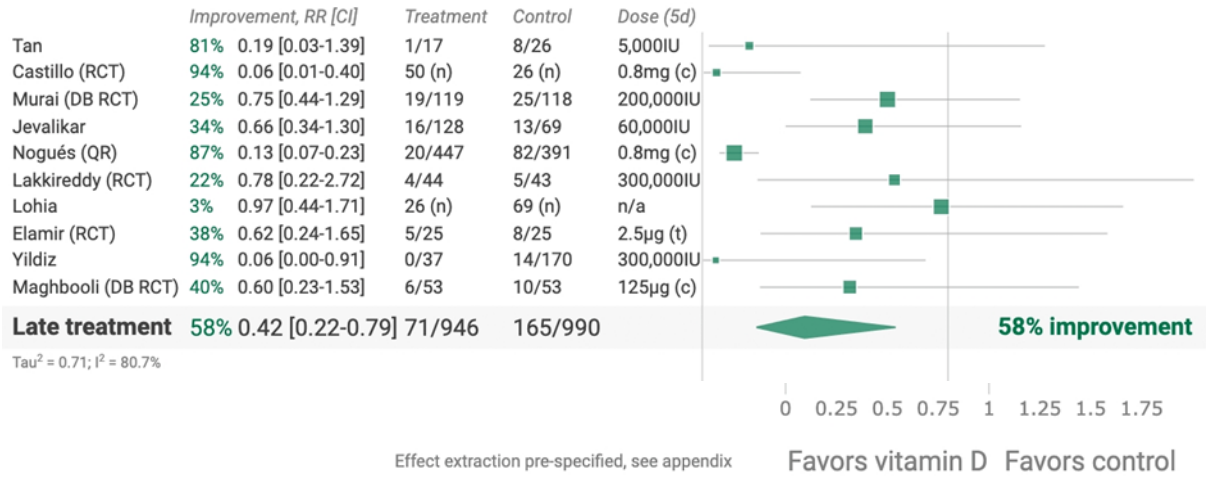


3.3 Risk reduction for ICU admission with late treatment with cholecalciferol or calcifediol

In addition to the meta-analyses mentioned above, the risk of ICU admission was also investigated. There were 10 peer-reviewed studies that examined the risk of ICU admission after late treatment. A meta-analysis of these trials in Table 4 showed a significant risk reduction of 58% (RR 0.42 [0.22 - 0.79]).

Table 4. Peer-reviewed trials for risk of IC admission with late treatment with cholecalciferol or calcifediol. (Part of Figure 14 from ref. [1]).

(All associated references are given in ref. [1]).



Four of the peer-reviewed studies from Table 4 analyzed the risk of IC admission with late treatment with calcifediol. [8-11] The results of treatment with calcifediol were repeated in Table 5 in order of decreasing dose over the first five days. A dose as used in trials by Castillo et al. and Nogués et al. led to the most favorable result. Treatment consisted of 2 capsules of Hidroferol on day 1, 1 capsule on day 3, then 1 capsule on days 7, 15 and 30. However, the doses administered in the trials of *Elamir et al*. and Maghbooli *et al*. were much lower and led to a greater chance of IC admission compared to the study by Nogues *et al*. The risk of death in the case of these intervention studies in Table 6 were mutually comparable. However, due to the limited study sizes, only the study by Nogues *et al*. led to a significant result in terms of reduced risk of death. In the trial by Alcala-Díaz *et al*. from Table 3, comparable doses were used as in Nogues *et al*. The risk of death was also comparable for these two studies.

Table 5. Peer-reviewed trials for risk of IC admission with late vitamin D treatment. (Part of Figure 14 from ref. [1]).

	Improvement	*RR [CI]*	*Treatment*	*Control*	*Dose (5d)*	*Reference*
Castillo (RCT)	94%	0.06 [0.01-0.40]	50 (n)	26 (n)	0.8 mg	[8]
Nogués (QR)	87%	0.13 [0.07-0.23]	20/447	83/391	0.8 mg	[9]
Elamir (RCT)	38%	0.62 [0.24-1.65]	5/25	8/25	0.0025 mg (t)	[10]
Maghbooli (DB RCT)	40%	0.60 [0.23-1.53]	6/53	10/53	0.125 mg (c)	[11]

Table 6. Peer-reviewed trials for risk of death or severe course with late treatment with calcifediol. Selection from Table 1 (Figure 9 of ref. [1]).

	Improvement	*RR[CI]*	*Treatment*	*Control*	*Dose (5d)*	*Reference*
Castillo (RCT)	85%	0.15 [0.01-2.93]	0/50	2/26	0.8 mg	[8]
Nogués (QR)	79%	0.21 [0.10-0.43]	21/447	62/391	0.8 mg	[9]
Elamir (RCT)	86%	0.14 [0.01-2.63]	0/25	3/25	0.0025 mg	[10]
Maghbooli (DB RCT)	40%	0.60 [0.15-2.38]	3/53	5/53	0.125 mg	[11]

3. Scientific evidence

Scientific evidence is available at different levels. [12] The trials listed above are all scientific peer-reviewed publications, in which the effect of treatment was compared with the effect of no treatment. A strong selection is often applied in which only the results of randomized studies are considered, ie the patients were randomly eligible for treatment or no treatment. Only nine of the 47 discussed trials were classified as RCTs.

The highest level of scientific evidence is provided upon acceptance by Cochrane Database of Systematic Reviews. Ethical considerations are not included in this. In this hectic time of pandemic, another serious objection is that the latest analysis on vitamin D and COVID-19 in early December 2021 is only up to date until 11 March 2021. Only three RCTs were involved in that analysis (Castillo, Nogues and Murai). The study by Nogués was not included because the patients were not randomized per person, but were randomized according to COVID ward at the hospital in Barcelona. In addition, during the latest analysis by Cochrane, an earlier version of Nogués' article had been pulled from the preprint server. [13] The important study by Nogués is now available online from 7 June after peer review. Due to the careful but lengthy procedures, the analyzes of five other RCTs that appeared after March 11 are not yet available.

Other organizations in the Netherlands that provide clinicians with study results for, among other things, vitamin D are the Antibiotic Policy Working Group (SWAB) and the Federation of Medical Specialists (FMS).

- SWAB only mentions the RCT studies of Castillo, Rastogi, Murai and Elamir in its most recent overview on the website (1 December 2021). Furthermore, it is not stated here that calcifediol is now approved in the Netherlands as Hidroferol.
- In its extensive overview of RCTs, FMS also only mentions the studies of Castillo, Rastogi, Murai and Elamir. Moreover, they have stopped adding information from RCTs regarding vitamins C and D, among other things, since September 2, 2021.

4. Discussion and conclusion

The available peer-reviewed intervention studies with early or late additional treatment with cholecalciferol or calcifediol show a significant benefit for the patient in terms of mortality risk and chance of admission to the ICU. In cases of hospitalization due to COVID-19, direct treatment with calcifediol according to Castillo *et al*. [8] and Nogués *et al*. [9] gives both a significant reduction in the risk of death as well as the lowest chance to need admission to ICU. In view of the identified bottlenecks in patient care, this appears to be a valuable option despite not meeting the strictest requirements of randomization. Ethical considerations can also form the basis for a decision to apply earlier. [14]

The intervention studies were conducted before vaccinations were introduced. None of the studies show that the administration of cholecalciferol or calcifediol is significantly harmful to the patient. The meta-analyses show that vitamin D supplementation had a beneficial effect on the course of COVID-19. An important finding is that the immune system was also able to contribute to a favorable course after infection with COVID-19 without prior knowledge of this virus, even without a vaccine. It is to be expected that vitamin D supplementation also plays a protective role in the occurrence of new variants such as the omikron variant.

The previous question from the Health Council of the Netherlands whether vitamin D supplementation can have a beneficial effect on the prevention of COVID-19 appears to have been answered significantly with positive results in the prevention trials in Table 1, although not by RCTs. The trials with late treatment using calcifediol in particular provide much clearer evidence for a more favorable course.

Even in the current situation with a high vaccination rate, not only did the number of infections increase from October, but also the number of hospital and ICU admissions due to COVID-19 and the number of deaths. This may not be explained entirely by an increase in the number of infections among unvaccinated and vaccinated individuals and a decrease in the effectiveness of the vaccine, but in many cases also by a reduced immune system due to a vitamin D deficiency.

It may be known from the report of the Health Council of 2012 (p. 70 and 71) that a vitamin D deficiency mainly occurs in overweight people and people with a darker skin colour. [15] Last year's findings with the ICU population with COVID-19 symptoms seem to confirm the association with the results of treating a vitamin D deficiency.

Analysis of available data from the PREVEND study in Groningen from 1997-1998 shows that the number of people with a vitamin D deficiency can be expected to increase from October (see the bottom graph; 25(OH)D) [16] This fits well in the pattern of hospital and ICU admissions seen in recent weeks, which did not occur in the summer months of 2021.

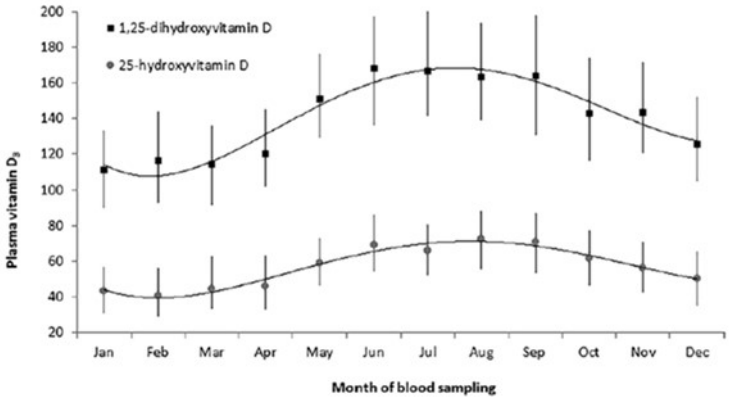


Figure 1. Plasma 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D concentrations by month of blood sampling in 5066 Prevention of Renal and Vascular End-Stage Disease participants. Values are mean and error bars represent the SD. Black squares represent 1,25-dihydroxyvitamin D in picomole per liter; grey circles represent 25-hydroxyvitamin D in nanomole per liter.

Figure 1. 25(OH)D and $1,25(OH)_2D$ in PREVEND study participants in Groningen.[16]

To prevent a vitamin D deficiency, the use of vitamin D supplements is of course preferred. But the current results show that recovery of the vitamin D status with calcifediol also offers good opportunities. This option has already been included in the list of medications for the treatment of vitamin D deficiency. Application could be extended to hospitalized patients with COVID-19.[5]

With respect to vaccination, taking additional measures is also of great importance. Vitamin D interventions are an important tool to support the immune system in those who have been vaccinated to improve the vaccination response. Now that we are in a crisis, we would do well to build on all the factors that support a well-functioning immune system and help to reduce the risk of infection, its severity and its duration. [17,18]

It can be concluded that supplementation with vitamin D and/or hidroferol is a safe, effective and inexpensive way to support optimal immune function and vaccine effectiveness. This may reduce the risk and especially serious consequences of infections such as COVID-19. In our opinion, it is desirable for both the patients and the IC capacity to make it possible to use calcifediol in addition to the usual medication in hospitalization with COVID-19 complaints, and to use the doses as applied by Castillo *et al*. and Nogues. *et al*. (2 capsules of Hidroferol with 0.266 mg of calcifediol each on day 1, 1 capsule on day 3, and 1 capsule on days 7, 15, and 30). [8,9] Furthermore, we think it is desirable to publicly announce that vitamin D is not only good for bone health, but also for strengthening the immune system. This increases the chances of a less serious course of an infection with COVID-19 and a reduction of the pressure on healthcare.

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