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Geriatr Psychol Neuropsychiatr Vieil 2020; xx (x): 1-10

Vitamin D and Covid-19 supplementation: expert consensus and recommendations

Vitamin D supplementation and COVID-19: expert consensus and guidelines

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Summary. After 12 months of viral circulation, SARS-CoV-2 has infected millions of people around the world, killing hundreds of thousands. In the absence of effective curative, preventive or vaccine treatment available to date against Covid-19, using existing drugs could help curb the pandemic. Vitamin D is a possible candidate discussed in numerous publications. Clinical trials randomized studies show that vitamin D supplementation significantly reduces the risk of respiratory infections. There are also many arguments suggesting that hypovitaminosis D is an independent (and easily modifiable) risk factor severe forms of Covid-19 and mortality from Covid-19. Vitamin supplementation mine D is a simple, risk-free, inexpensive measure reimbursed by insurance disease, which is effective in correcting hypovitaminosis D found in 40 to 50% of French population and in more than 80% of adults with Covid-19. In this paper position, we offer simple vitamin D supplementation regimens at adults in the absence or in the event of Covid-19.

Keywords: Covid-19, SARS-Cov-2, vitamin D, supplementation, recommendations

Abstract. *After 12 months of viral circulation, the SARS-CoV-2 has infected millions of people around the world, leaving hundreds of thousands dead. With the lack of effective therapy and vaccination against COVID-19, focusing on the immediate repurposing of existing drugs gives hope of curbing the pandemic. Vitamin D is a possible candidate discussed in a high amount of publications. Randomized clinical trials show that vitamin D supplementation significantly reduces the risk of respiratory infections. There are also many evidences that hypovitaminosis D is an independent (and easily modifiable) risk factor for severe forms of COVID-19 and death. Vitamin D supplementation is a simple, safe and inexpensive measure, which is effective in correcting hypovitaminosis D found in 40-50% of the French population and in more than 80% of adults with COVID-19. In this position paper, we propose simple regimens (adapted to the pharmaceutical forms currently available in France) for vitamin D supplementation in adults with or without COVID-19.*

Key words: *COVID-19, SARS-CoV-2, vitamin D, supplementation, guidelines*

The 're coronaviruses are a large family single-stranded RNA viruses, which infect animals and humans. Since December 2019, the disease coronavirus 2019 (Covid-19) caused by coronavirus 2 severe acute respiratory syndrome (SARS-CoV-2; aupa-ravant 2019-nCoV) is spreading around the world. The virus is transmitted mainly through close contact,

While the majority of cases only result in symptoms mild, some progress to distress syndrome acute respiratory (ARDS) associated with a significant increase in high and uncontrolled blood levels of cytokines and chemokines. This "cytokine storm", apparently secondary to the downregulation of the converting enzyme Zion of type 2 angiotensin (ACE2) by SARS-CoV-2,

most often via small droplets produced by coughing, sneezing, and talking. The Covid-19 is characterized by fever, cough, pneumonia severe associated with the occurrence of frosted glass opacities, thrombosis and endothelitis, and a wide variety clinical signs including major asthenia and cardiac, neurological or digestive signs [1, 2].

is at the origin of a strong pro-inflammatory environment-associated with severe tissue damage, contributing to ARDS and severe forms of Covid-19 [3]. The people elderly and those with co-morbidities such as high blood pressure, diabetes or obesity are more at risk develop a serious, even fatal, form of Covid-19, with an estimated mortality rate of less than 1.1% in

v.2020.0907
doi: 10.1684 / pn

To cite this article: Annweiler C, Souberbielle JC. Vitamin D and Covid-19 supplementation: expert consensus and recommendations. *Geriatr Psychol Neuropsychiatr Vieil* 2020; xx (x): 1-10 doi : 10.1684 / pnv.2020.0907

under 50 and increasing after that age up to around 30-35% in very elderly frail people and polymorbides [4].

After 12 months of viral circulation, the Covid-19 has now but affected millions of people around the world, killing hundreds of thousands. Without curative, preventive or vaccine treatment effective to date [1], using existing drugs could help to stem the pandemic. In this perspective, an explosion ration *in silico* very early on identified vitamin D among the three molecules most likely to reduce the effects of Covid-19 through its effects on gene expression [5].

What elements put on the vitamin D trail?

Vitamin D is naturally synthesized by the skin during summer exposure to ultraviolet B (UVB) rays solar. The vitamin D status of an individual is defined by its circulating concentration of 25-hydroxyvitamin D (25 (OH) D). Deficiency, defined by a circumscribed concentration culante 25 (OH) D less than 12 ng / mL (or 30 nmol / L), and vitamin D insufficiency, defined by a concentration circulating level of 25 (OH) D less than 20 ng / mL (or 50 nmol / L), are therefore more frequent in winter from October to March above 28 degrees north [6, 7]. That corresponds precisely at the latitudes where the highest death rates high levels of Covid-19 were observed during the first winter months of 2020 [8]. In the past, coronaviruses and influenza viruses had already shown a very strong seasonality, with preferential winter appearances in the northern hemisphere [9].

Contrary to popular belief, vitamin D is not a vitamin, but rather a steroid hormone which the effects are not only centered on the regulation tion of calcium metabolism and prevention of fractures bone [6, 7]. For example, several works have mon- very positive effect of vitamin D supplementation on the prevention of acute respiratory infections, including -47; -83%] ($p < 0.001$), when daily doses or weekly were administered to individuals deficient in vitamin D.

Likewise, circulating concentrations of 25 (OH) D are directly associated with endothelial functioning [12], whose systemic inflammatory disease during Covid-19 affects the lungs, but also the heart, kidneys, intestine and brain and could explain the diversity of symptoms observed in this infection [13].

These various observations quickly brought to light to manage the idea, from March 2020, that the vitamin D could be of interest against Covid-19, at the times to reduce the incidence of infection [14], but also to reduce the intensity of symptoms in the forms severe [15, 16]. On the date of our article submission (25/11/2020), the search on PubMed associated with the request "Vitamin D AND COVID-19" found 304 references.

What role could the vitamin play D against SARS-CoV-2?

Vitamin D is a secosteroid hormone [6, 7]. In binding to vitamin D response elements (VDRE) located in the promoter region of different genes, including expression is thus either activated or repressed, the vita- mine D can theoretically prevent and / or improve severe forms of Covid-19 by regulating: 1) the system renin angiotensin (RAS), 2) innate cellular immunity and adaptive, 3) physical barriers, and 4) fragility and Host comorbidities [16].

First, vitamin D reduces permeability pulmonary in animal models of ARDS in modu- lant activity of SRA and expression of ACE2 [17, 18]. This action is crucial, as SARS-CoV-2 appears to be useful read ACE2 as a receptor to infect cells hosts [3] and downregulates the expression of ACE2 [19] . ACE2 is expressed in many organs, including endothelium and alveolar epithelial cells

flu [10] , as well as an improvement in symptoms, in case of proven infection [11]. The results of the meta-analysis by Martineau *et al.* [10], which included individual data intention-to-treat for almost 11,000 patients from 25 randomized controlled trials, concluded a 12% reduction in the risk of respiratory infections acute [95% confidence interval (95% CI): 4; 19%] ($p < 0.001$). Pre-specified analyzes in subgroups showed that reducing the risk of respiratory infections was the most important, reaching -70% [CI95:

lungs, where it has protective effects against inflammation. During Covid-19, negative regulation ACE2 causes an inflammatory chain reaction, cytokine storm, complicated by ARDS [1, 3]. At Conversely, a study in rats with ARDS chemically induced has shown that administration of vitamin mine D increased mRNA and ACE2 protein levels [20], and that rats supplemented with vitamin D present had milder ARDS symptoms and lesions pulmonary more moderate than the controls.

Second, many studies have described the antiviral effects of vitamin D, which acts either by inducing tion of antimicrobial peptides with antiviral activity direct against enveloped and non-enveloped viruses, either by immunomodulatory and anti-inflammatory effects [21]. These effects are potentially important for Covid-19 to limit the cytokine storm. Vitamin D could prevent ARDS [22] by reducing the production of pro-inflammatory cytokines by T helper lymphocytes type 1 (Th1) such as interleukin-6, *tumor necrosis factor* (TNF) and interferon [21]. It also increases the expression of anti-inflammatory cytokines by macrophages [21].

Third, vitamin D stabilizes the physical barriers sics [15]. These barriers are made up of cells closely linked to prevent external agents (such viruses) from reaching tissues susceptible to infection. Although viruses alter the integrity of the cell junction, vitamin D helps maintain tight junctions functional via E-cadherin [15].

Fourth, several studies suggest that hypovitaminosis D is a risk factor for severe Covid-19 [16, 23-25], as the risk factors hypovitaminosis D, but also chronic diseases that accompany it are very similar to the risk of severe form of Covid-19 [1, 6, 7] . This point is potentially very interesting because, unlike other risk factors for severe form of Covid-19 (advanced age, obesity, multiple comorbidities) [1] on the- which there are few (or no) possibilities to act, hypovitaminosis D is a risk factor very easily modifiable by simple supplementation.

Low concentrations vitamin D in people with Covid-19

mean circulating concentrations of 25 (OH) D in the population general and the number of Covid-19 cases, as well as with the Covid-19 death rate in these countries [28]. Concerning the chronological sequence, it has been reported that hypovitaminosis D precedes and predicts the incident occurrence of Covid-19 (*hazard ratio* (HR) = 1.56 with $p < 0.001$ in case of 25 (OH) D initial < 10 ng / mL, and HR = 1.33 with $p < 0.001$ in case of 25 (OH) D between 10 and 20 ng / mL) [29]. In case of proven infection, the existence of a hypovitamin D appears to be directly associated with the prognosis of Covid-19 since the cases of Covid-19 with hypovitaminose D are more likely to have a form severe (relative risk 1.59 with $p = 0.02$ in the case of 25 (OH) D < 30 ng / mL) [30], to require the use of ventilanon-invasive [31], to have a length of hospital stay prolonged [27], and to die from Covid-19 [29, 30]. For more details, the review by Mercola *et al.* list of exhaustively and critically the various studies on the association between 25 (OH) D concentration and prognosis of Covid-19 [24]. Overall, these results suggest that low circulating concentrations of 25 (OH) D increase the risk of severe forms of Covid-19. At on the contrary, the increase in 25 (OH) D could prevent and / or improve severe forms of Covid-19.

Vitamin D supplementation could have a preventive effect and / or curative against Covid-19

Vitamin D supplementation before SARS-CoV-2 infection

Two quasi-experimental studies report less severe forms of Covid-19 and better survival in case of regular vitamin D supplementation, especially if the last take is recent.

The first study, conducted in 77 elderly patients

Many observational studies have been
driven in record time. For example, the first
authors who measured circulating 25 (OH) D in
patients tested for SARS-CoV-2 infection found
that the cases of Covid-19 had, on average, concentrations
trations of 25 (OH) D more than twice as low as
non-Covid-19 controls (respectively, 11.1 ng / mL
versus 24.6 ng / mL, p = 0.004) [26]. Other authors have
since reported that 82.2% of patients hospitalized for
Covid-19 had circulating 25 (OH) D < 20 ng / mL
[27]. Similarly, significant inverse correlations have
been found in 20 European countries between the concentra-
pitted for Covid-19 in an acute geriatric ward
French during the first wave, reports that the
patients regularly supplemented with vitamin D before
their infection had a 93% lower risk of dying
14 days from Covid-19 compared to those who were not
supplemented (HR = 0.07 with p = 0.017) [32]. The supplements
The elements used here were based on either a dose of 50,000
IU *oral* vitamin D3 per month, on a dose of
80,000 or 100,000 IU *per os* every 2-3 months.

The second study involved 66 residents of an nursing home
French people infected with Covid-19 during the first wave
[33]. Residents were all vitamin supplemented

Long-term D3 at a rate of 80,000 IU *per os* every 3
month. The analysis looked at the temporality of the sup-
implementation and showed that residents who had received u
their vitamin D supplement in the previous month
infection had an 89% greater 14-day survival rate
higher than those who had received it within two or three
previous months (HR = 0.11 with p = 0.003).

More recently, these studies have been supported by
preliminary results of the Koronastudien.no study in Nor-
vège showing that regular consumers of
cod liver were at lower risk of infection.
by SARS-CoV-2 and, if infected, develop
a severe form of Covid-19 [34].

There is thus a scientific presumption that the contribution
regular vitamin D has an interest in improving the
prognosis of Covid-19 and avoid severe forms (par-
especially when the last shot is recent and closest
possible infection, which implies concentration
of 25 (OH) D high at the time of contamination), even
to prevent infection.

At this point, however, there is no evidence yet
scientific indisputable in the absence of clinical trial well
led. The results of randomized controlled clinical trials
against placebo, such as the Cod Liver Oil Study which will include
70,000 people in Norway (ClinicalTrials.gov Identifier:
NCT04609423), are expected to determine with a high
level of evidence the effect of regular vitamin D intake
on the incidence of Covid-19.

Vitamin D supplementation in case of SARS-CoV-2 infection

Although regular intake of vitamin D before infection
appears beneficial, it is however important to note
that the results of previous studies also show
than supplementation with standard doses of vitamin
those who only received standard care (1/50 or 2%
against 13/26 or 50%; p < 0.001), suggesting a preven-
tion of severe forms of Covid-19 by this metabolite of
vitamin D. In France, the multicentre randomized controlled trial
COVIT-TRIAL, started in April 2020, tests the effect of
high dose of 400,000 IU of vitamin D3 *per os* on survival
to 14 days of elderly people with Covid-19 compared to
port at a standard dose of 50,000 IU of *oral* vitamin D3
(ClinicalTrials.gov Identifier: NCT04344041) [36]. The recruit
is still in progress and inclusions should
be completed within the next few weeks. The results
could shed important light on the cura-
effective vitamin D activity in people who already have
of Covid-19.

Should you supplement with vitamin D to fight against Covid-19?

Before considering the fight against Covid-19, it seems
logic to avoid vitamin D deficiency that we know
the deleterious effect on, at least, bone and neuro-health
muscle [6, 7]. The most recent studies using
the best possible methodology (meta-analyzes using
the individual data of all patients included in
intervention studies + use of the
25 (OH) D assay reference) concluded that for
that 97.5% of the general population have a
circulating tration of 25 (OH) D > 20 ng / mL, intakes
daily vitamin D should be 1200 IU (30 g)
at least [37], that is to say much higher than the
Recommended daily allowance (RDA) or that the
French nutritional advice (ANC). We can see that this
is not followed in practice since around 40 to 50% of
the general French population has a circulating 25 (OH) D

mine D after the diagnosis of Covid-19 was not associated to better survival [32]. The whole question then is know what could be offered to infected people not having received vitamin D supplements until then. Randomized clinical trial results awaited to answer with a high level of evidence to this question tion of curative benefit. Thus, in Spain, a study randomized pilot compared the prognosis of 76 adults young people (average age, 53; 40.8% women) hospitalised for Covid-19 and having received either supplements calcifediol (i.e. 25 (OH) D) in addition to treatment standards against Covid-19, i.e. only healthcare standards [35]. The results of this study showed that the group of patients who received the high dose of calcifediol used significantly less resuscitation than

< 20 ng / mL [38]. In fact, French learned societies have been encouraging since 2011 to supplement with vitamin D the most fragile people over 65 and in loss of independence [39], *a fortiori* those residing in Ehpad [40]. Supplementation without pre-dosing lable should also be offered to pregnant women as soon as early pregnancy, and children and adolescents throughout growth [41].

Concerning more specifically the promotion of vitamin D supplementation in order to act on the prevention and / or evolution of Covid-19, several companies national and international scholars have published articles of "position" encouraging this supplementation [42-45]. In the UK, the government is also taking this lead seriously and plans to provide during the winter of 2021

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vitamin D supplements for more than two million people fragile rings to better protect them against Covid-19 [46].

What attitude to adopt in practice with regard to supplementation in vitamin D before any infection by SARS-CoV-2?

The dosage of 25 (OH) D is not useful (and not reimbursed) in the general population, in whom the target concentration is between 20 and 60 ng / mL [47]. On the contrary, it is necessary in individuals for whom the target concentration is between 30 to 60 ng / mL: 1) patients in a situation of "bone fragility" (defined by a mineral density low bone and / or a "low energy" fracture and / or in case of taking treatment or potential illness-responsible for bone fragility); 2) patients chronic renal failure from stage 3b (flow of glomerular filtration < 45 mL / min / 1.73 m 2); 3) patients suffering from malabsorption (celiac disease, disease of Crohn's, rectocolic hemorrhagic, cystic fibrosis ... ; “malabsorptive” bariatric bypass surgery, *etc.*); 4) elderly patients who fall [48, 49]. In these situations, the dosage of 25 (OH) D is justified by the very large interindividual variability of response to supplementation tion in terms of increasing the concentration of 25 (OH) D, which prevents setting a dosage of vitamin D that would allow the entire population to reach a concentration of 25 (OH) D between 30 and 60 ng / mL without prior dosage.

D, a pathway for inactivating vitamin D, the first of which step is hydroxylation on carbon 24, is stimulated [50]. In addition, the prevention of respiratory infections by vitamin D supplementation is currently not found only with moderate daily doses [10]. In France, to our knowledge, there is no form pharmaceutical vitamin D for administration simple daily ration (dosed for example at 1,000-1,200 IU) apart from very low dose drops used in newborns. An assessment of the quality of the foods containing vitamin D available in France seems necessary to us before recommending some. Clinical practice is therefore always based on the prescription of spaced boluses (ampoules of 50,000 IU, 80,000 IU, 100,000 IU or 200,000 IU).

For these different reasons, we recommend distinguish, before any infection with SARS-CoV-2:
- healthy adults, for whom natural intakes (especially sun exposure) are sufficient between May and October, but for whom regular supplementation height (ideally) of 1,000-1,200 IU / day or, failing that, 50,000 IU / month is reasonable between November and April in due to the absence of UVB over this period at latitudes French. Several studies have shown that, in the absence shapes adapted to a daily setting, a spacing less than or equal to one month makes it possible to stabilize the tration of 25 (OH) D provided that vitamin D3 is used (and not vitamin D2 whose half-life is much more short) [47] . The monthly frequency also appears adapted to the context of Covid-19, by ensuring regular vitamin D and, therefore, temporally not too much away from possible infection [33];
- adults under 65 at high risk

Regarding supplementation, it should be remembered that half of the general population has an inferior 25 (OH) D greater than 20 ng / mL [38]. In other words, supplement everything the world would be like administering supplementation to about 50% of people who probably don't have one need; on the contrary, not supplementing anyone would come back to neglect about 50% of the population who could potentially tially benefit from this supplementation. The solution is therefore to adopt a supplementation strategy risk function (*Table 1*).

It will also be noted that, compared to the supplement spaced bolus therapy, daily supplementation by moderate doses is theoretically to be favored, because more physiological. Even if we do not clearly know the mechanism, the skin limits the synthesis of vitamin D3 to approximately 10,000 IU per day (however variable from one individual to another) when exposed to the sun. Several studies have shown that after taking a high dose of vitamin

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Table 1. Vitamin D supplementation scheme in adults.
Table 1. *Vitamin D supplementation in adults.*

In healthy adults, regardless of age	• 25 (OH) D concentration objective to be reached: 20 ng / mL (50 nmol / L) • Sufficient natural intake between May and October: outdoor activities, sun exposure for between 15 and 30 minutes per day of the arms and legs without sun protection, varied diet • No systematic dosage of circulating 25 (OH) D • Supplementation for everyone in France between November and April: ideally 1,200 IU / day; failing that, 50,000 IU / month of vitamin D3 *per os*
In adults under 65 with dosage of 25 (OH) D < 30 ng / mL or high risk hypovitaminosis D (sick or fragile or dependent or obese) or at risk of osteoporosis	• 25 (OH) D concentration objective to be reached: 30 ng / mL (75 nmol / L) • Insufficient natural intake, but to be encouraged • Charging supplement: - if 25 (OH) D < 20 ng / mL: 8 doses of 50,000 IU of vitamin D3 *per os* 7 days apart - if 25 (OH) D between 20 and 30 ng / mL: 4 doses of 50,000 IU of vitamin D3 *per os* 7 days apart • In all cases, followed by maintenance supplementation
In adults over 65 years with dosage 25 (OH) D < 30 ng / mL or at high risk hypovitaminosis D (very old ≥ 80 years or ill or frail or dependent or obese or alive in Ehpad)	• 25 (OH) D concentration objective to be reached: 30 ng / mL (75 nmol / L) • Insufficient natural intake, but to be encouraged • Charging supplement: - 80,000 IU or 100,000 IU of vitamin D3 *per os* every month for 3 month • In all cases, followed by maintenance supplementation
Maintenance supplementation	• Objective of 25 (OH) D concentration to maintain: 30 ng / mL (75 nmol / L) • Insufficient natural intake, but to be encouraged • Maintenance supplement: - if BMI < 30 kg / m 2 : 50,000 IU of vitamin D3 *per os* every month - if BMI > 30 kg / m 2 : 80,000 IU of vitamin D3 *per os* every month • After 6 to 9 months under maintenance treatment, re-dose 25 (OH) D: - if 25 (OH) D < 30 ng / mL: either reduce the interval between doses (for example, 50,000 IU every 2 weeks) or increase the dosage (for example, 80,000 or 100,000 IU per month) - if 25 (OH) D > 60 ng / mL (rare): space the intakes further (for example, 50,000 IU every 2 months) pending possible availability less dosage forms

the objective of maintaining concentration over the long term

If we agree in theory with the recom-

hypovitaminosis D (sick, or fragile, or dependent, or obese) or at risk of osteoporosis or having a of blood showing a concentration of 25 (OH) D < 30 ng / mL, for whom supplementation should be based on rapid recharge of vitamin D3 over 2 to 4 weeks [47], immediately followed by maintenance supplementation aiming to maintain the concentration of 25 (OH) D above 30 ng / mL using the posolo- lowest among pharmaceutical forms available (today 50,000 IU) and as much as possible short interval of one month maximum between two catches;

- adults over 65 at high risk hypovitaminosis D (very old ≥ 80 years, or sick, or fragile, or dependent, or obese, or living in nursing homes) or having a blood test showing a concentration of 25 (OH) D < 30 ng / mL, for whom supplementation is based on a recharge of vitamin D stocks over 2 months [51], followed by lifelong maintenance supplementation with

of 25 (OH) D above 30 ng / mL.

What attitude to adopt in practice vis-à-vis supplementation in vitamin D in case diagnosis of Covid-19?

In the event of a proven Covid-19, the Academy of Medicine recommends in France since May 22, 2020 [52]:
- quickly measure the level of 25 (OH) D circulating in people over 60 years of age upon confirmation diagnosis of Covid-19, and administer, in the event of deficiency, a loading dose of 50,000 to 100,000 IU;
- to provide vitamin D supplementation of 800 to 1000 IU / day in people under the age of 60 upon confirmation of the diagnosis of Covid-19.

mandate of the Academy of Medicine to supplement in vitamin D Covid-19 patients according to dosage of circulating 25 (OH) D [49] , we are also aware of are aware that this assay result could in many cases case to be available only after a delay in our opinion. ceptable, in the hospital as in town. For example, and then that the administration of a bolus of vitamin D appears urgent in this infectious context, the realization of a outpatient blood sampling includes several steps (making an appointment in a medical analysis laboratory, trip to the laboratory, waiting for the analysis result may take several days, communication of the result report to the attending physician, writing the prescription to fax at the pharmacy, and patient travel to find supplement) which may discourage patients, and this all the more so as they should remain isolated because of their Covid-19. Similar difficulties can be encountered regions in nursing homes that do not have a pharmacy for indoor use. In hospital, the severity of the Covid-19 (suf- important to have motivated the hospitalization)

Table 2. Vitamin D supplementation in adults with Covid-19, regardless of age and when the concentration of 25-hydroxyvitamin D is not known * .
Table 2. *Vitamin D supplementation in adults with a diagnosis of COVID-19, regardless of age and when 25-hydroxyvitamin D concentration is not known * .*

	Last administration < 1 month	**Last administration > 1 month**	**Risk factors severity of Covid-19 †**
Adults regularly vitamin D supplement	Loading dose 100,000 IU of vitamin D3 *per os, to renew after 1 week*	Loading dose 200,000 IU of vitamin D3 *per os, to renew after 1 week*	Loading dose 200,000 IU of vitamin D3 *per os, to renew after 1 week*
Adults usually no vitamin D supplement	Loading dose of 200,000 IU of vitamin D3 *per os, to renew after 1 week*		

* Ideally, it would make sense to dose circulating 25 (OH) D and supplement depending on the result, as proposed by the Academy of Medicine. In practice, the delay to obtain the result of the dosage in a majority of situations encourages us to propose the supplementation without waiting for the result of the 25 (OH) D assay. † Cardiovascular history, obesity, chronic respiratory failure, severe renal failure, NYHA heart failure III or IV, cirrhosis ≥ stage B, insulin-dependent diabetes, immunosuppression, cancer or blood disease.

also most often invalidates the possibility of waiting until the result of the 25 (OH) D assay.

Based on the safety of vitamin D (see more low) and on the results published since May 2020 confirming the existence of a cause and effect relationship between the vitamin D and the prognosis of Covid-19 according to the Bradford criteria Hill [16, 24], this observation of “real life” leads us to propose, whatever the age and without waiting for the result of a possible dosage of 25 (OH) D:
- in adults regularly supplemented with vitamin mine D and whose last administration dates less than

Table 3. Vitamin D supplementation in affected adults of Covid-19 when the concentration of 25-hydroxyvitamin D (25 (OH) D) is known regardless of age and factors of severity of Covid-19.
Table 3. *Vitamin D supplementation in adults with a diagnosis of COVID-19 when the 25-hydroxyvitamin D (25 (OH) D) concentration is known, regardless of age and COVID-19 severity factors.*

	Supplementation in vitamin D3 *per os* upon confirmation of the diagnosis of Covid-19
Si 25 (OH) D lower at 20 ng / mL	1 loading dose of 200,000 IU, to be renewed

from 1 month: a loading dose of 100,000 IU of vitamin D3 *per os* upon confirmation of the diagnosis of Covid-19, at renew after a week;
- in adults not usually supplemented with vitamin D or whose last administration is older from 1 month: a loading dose of 200,000 IU of vitamin D3 *per os* upon confirmation of the diagnosis of Covid-19, at renew after a week;
- in adults who are obese and / or have other Covid-19 severity risk factors (history cardiovascular, chronic respiratory failure, heart failure severe renal impairment, NYHA III heart failure or IV, cirrhosis ≥ stage B, insulin-dependent diabetes, immune depression, cancer or blood disease): a loading dose of 200,000 IU of vitamin D3 *per os* upon confirmation of the diagnosis of Covid-19, to be renewed after one week (*table 2*).

If the measurement of 25 (OH) D is known, we propose, whatever the patient's age and risk factors severity of Covid-19:
- in the event of a 25 (OH) D concentration of less than 20 ng / mL: a loading dose of 200,000 IU of vitamin D3 *per os* upon confirmation of the diagnosis of Covid-19, at renew after a week;
- in the event of a 25 (OH) D concentration between 20 and 30 ng / mL: a loading dose of 100,000 IU of vitamin D3 *per os* upon confirmation of the diagnosis of Covid-19, at renew after a week;
- in the event of a 25 (OH) D concentration between 30 and 40 ng / mL: a loading dose of 50,000 IU of vitamin D3 *per os* upon confirmation of the diagnosis of Covid-19, at renew after a week;
- in the event of a 25 (OH) D concentration greater than 40 ng / mL: no loading dose (*Table 3*).

	after a week
Si 25 (OH) D included between 20 and 30 ng / mL	1 loading dose 100,000 IU, to be renewed after a week
Si 25 (OH) D included between 30 and 40 ng / mL	1 loading dose of 50,000 IU, to be renewed after a week
Si 25 (OH) D greater at 40 ng / mL	No loading dose

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This supplementation makes it possible to quickly obtain satisfactory vitamin D status during the period critical for about a month during which patients with Covid-19 can report serious forms [1]. The interest of higher dosages is currently under study [36] . The dosage of the second dose (in second week of Covid-19) can be adjusted depending on tion of a possible dosage of 25 (OH) D at 7 days of first take.

Once the acute phase of Covid-19 has passed, the diagram supplementation may follow the recommendations of the *table 1* from the following month.

What are the risks of vitamin D supplementation?

Vitamin D supplementation respecting the prescription regimens proposed here do not present in theory ries no particular risk, apart from clinical situations rare (sarcoidosis and other granulomatosis) or very rare (inactivating mutation of certain genes such as CYP24A1 [Cytochrome P450 Family 24 Subfamily A Member 1]). Poisoning is extremely rare (less than 1 per 20,000 according to the Mayo Clinic) and correspond to the appearance of hypercalcemia with possible manifestations

Key points

- Vitamin D can theoretically prevent and / or improve severe forms of Covid-19 by regulating the renin-angiotensin system, cellular immunity innate and adaptive, physical barriers, and frailty and host comorbidities.
- Adults with hypovitaminosis D have a increased risk of Covid-19.
- In the event of Covid-19, the existence of hypovitaminosis D is associated with a severe excess risk and mortality.
- In the absence of major risk associated with supplementation vitamin D, we recommend that you add ter people at risk throughout the year hypovitaminosis D, and the general population for the winter period.
- In the event of Covid-19, while awaiting the results status of controlled studies in progress, we propose to administer, upon diagnosis of Covid-19, a dose from 100,000 to 200,000 IU of vitamin D3 *per os* at once, to be renewed after week.

clinical conditions (calcium lithiasis and / or nephrocalcinosis). Poisoning never occurs for concentrations trations of 25 (OH) D < 150 ng / mL (375 nmol / L), nor for supplementation dosages less than 4000 IU / day (100 g / day), or even 10,000 IU / day (250 g / day) [53], and are linked to considerable catches in autumn. dication or prescription errors (for example 100,000 IU / day instead of 100,000 IU / month). A fear frequent related to the prescription of vitamin D, in particular bind without prior assay and therefore without confirmation of the existence of hypovitaminosis D, concerns the risk of renal lithiasis. Large recent clinical trials control However, the versus placebo are reassuring on this point, and clearly showed that there was no increase renal lithiasis in patients without vitamin D (with an average 25 (OH) D of around 30 ng / mL at baseline in studies) that received pen- for several years 2000 IU / day [54] or 4000 IU / day vitamin D3 [55].

Conclusion

Hypovitaminosis D, found in 40 to 50% of French population [38], constitutes a risk factor independent of Covid-19 which has the advantage of being very easily modifiable by medication supplementation liar. Vitamin D supplementation is a simple, effective, inexpensive measure reimbursed by health insurance. In the absence of major risk associated with supplementation, and even if the impact on prevention tion and / or improvement of severe forms of Covid-19 makes still the subject of studies in progress, everything is growing today supplement with vitamin D throughout the year people at risk of hypovitaminosis D, and the popula- general tion during the winter period. This attitude in fact corresponds to respecting the recommendation (except Covid-19) to maintain a satisfactory vitamin D status in everyone, and therefore does not require waiting the results of randomized controlled trials dedicated to Covid-19 to be applied. In case of Covid disease- 19 found in an adult patient while awaiting results of the dedicated tests in progress, we offer to administer, upon diagnosis of Covid-19 and regardless of or age, a loading dose of 100,000 to 200,000 IU of vitamin D3 *per os* at once, to renew afterwards one week.

Links of interest: C. Annweiler is an occasional consultant for the Mylan laboratory and principal investigator of the COVIT-TRIAL trial. The authors declare that they have no link of interest in relation to this article.

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