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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 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, most often via small droplets produced by

're coronaviruses are a large family single-stranded RNA viruses, which infect animals and humans. Since December 2019, the disease

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 levels of cytokines in the blood and chemokines. This "cytokine storm", apparently secondary to the downregulation of the converting enzyme Zion of angiotensin type 2 (ACE2) by SARS-CoV-2, is at the origin of a strong pro-inflammatory environment-

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 of clinical signs including major asthenia and cardiac, neurological or digestive signs [1, 2] .

associated with severe tissue damage, contributing to the 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

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under 50 and increasing after that age up to about 30-35% in frail very old 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 attenuate 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 of 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 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 osseous [6, 7] . For example, several works have mon- very positive effect of vitamin D supplementation on the prevention of acute respiratory infections, including 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 -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 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 submission of our article (25/11/2020), the search on PubMed associated with the query "Vitamin D AND COVID-19" found 304 references.

What role could the vitamin 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) frailty 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, because 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 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

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:

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 the 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 as 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] , because the risk factors hypovitaminosis D, but also chronic diseases that accompany it are very similar to the factors of 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

Numerous 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

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 incident occurrence of Covid-19 (*hazard ratio* (HR) = 1.56 with $p < 0.001$ in case of initial 25 (OH) D < 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 event of 25 (OH) D < 30 ng / mL) [30] , to require the use of ventilanon-invasive treatment [31] , to have a long 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 hospitted 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 ments 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

Covid-19 had circulating 25 (OH) D < 20 ng / mL [27] . Likewise, significant inverse correlations have been found in 20 European countries between the concentra- mean circulating concentrations of 25 (OH) D in the population

French people with Covid-19 during the first wave [33] . Residents were all supplemented with vitamin Long-term D3 at a rate of 80,000 IU *per os* every 3 month. The analysis focused on 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 take is recent and closest possible infection, which implies concentration of 25 (OH) D high at the time of contamination), or 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 D mine 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) hospi- talised 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

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 the insufficiency in vitamin D which 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 1,200 IU (30 g) at least [37] , that is to say much higher than the Recommended daily allowances (RDI) 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 < 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 vitamin D supplements for more than two million people

used significantly less resuscitation than the one who received only standard care (1/50 or 2% against 13/26 or 50%; p < 0.001), suggesting a preventive effect.

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 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 an increase in the concentration of 25 (OH) D, which prevents setting a dosage of vitamin D that would allow the entire population to reach a 25 (OH) D concentration between 30 and 60 ng / mL without prior dosage.

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 tiially 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 D, a pathway for inactivating vitamin D, the first of which step is a hydroxylation on carbon 24, is stimulated [50] . In addition, the prevention of respiratory infections by fragile rings to better protect them against Covid-19 [46] .

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 it 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 suitable for daily use, 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 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 levels 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 old, 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 as the objective of maintaining concentration over the long term

vitamin D supplementation is not currently

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

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

In healthy adults, whatever the 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 1200 IU / day; failing that, 50,000 IU / month of vitamin D3 *per os*
In adults under 65 years with dosage 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 high risk hypovitaminosis D (very old ≥ 80 years or sick or fragile or dependent or obese or living in nursing homes)	• 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	• 25 (OH) D concentration objective 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 of less dosed forms

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 the age of 60 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 1,000 IU / day in people under the age of 60 upon confirmation of the diagnosis of Covid-19.

If we agree in theory with the recommandate of the Academy of Medicine to supplement in vitamin D Covid-19 patients depending on the dosage 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 the supplement) which may discourage patients, 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) also most often invalidates the possibility of waiting until the result of the 25 (OH) D assay.

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 be renewed 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 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.

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 25 (OH) D assay:
- in adults regularly supplemented with vitamin mine D and whose last administration dates less than 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 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;

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 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

- 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*).

This supplementation makes it possible to quickly obtain satisfactory vitamin D status during the period critical of 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 and / or calcemia / calciuria 7 days after the first intake.

Once the acute phase of Covid-19 has passed, the scheme 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 The prescription regimens proposed here do not present in theories 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 exceedingly rare (less than 1 per 20,000 according to the Mayo Clinic) and correspond to the appearance of hypercalcemia with possible manifestations 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, against placebo are reassuring on this point, and clearly showed that there was no increase renal lithiasis in patients who are not deficient in vitamin D (with an average 25 (OH) D of around 30 ng / mL at baseline in studies) that received penfor 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] , is a risk factor independent of Covid-19 which has the advantage of being very easily modifiable by drug 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 ongoing studies, everything is growing today to supplement 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 the event of Covid disease 19 found in an adult patient, while awaiting results of the dedicated tests in progress, we offer to administer, from the diagnosis of Covid-19 and whatever or age, a loading dose of 100,000 to 200,000 IU of vitamin D3 *per os* in one go, to renew afterwards one week.

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 an increased risk of severe form 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 the 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.

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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