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Perspectives/Opinions

The Covid-19 infection: An opportunity to develop systematic vitamin D supplementation in psychiatry

L'infection à Covid-19 : une opportunité pour développer la supplémentation systématique en vitamine D en psychiatrie

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ABSTRACT

Psychiatric patients are at risk of hypovitaminosis D and Covid-19-related mortality. In addition to the mental health benefits, vitamin D supplementation may be potentially effective in preventing severe forms of Covid-19 infections. Vitamin D supplementation is not necessary and is not reimbursed in France for this indication. A monthly supplementation of 50,000 IU may be sufficient in most cases. Double the dose is recommended for obese patients. The risk of renal lithiasis is not increased at these doses, even when supplemented in a patient without vitamin D deficiency. The Covid-19 crisis is an opportunity to disseminate vitamin D supplementation in psychiatric patients, as it has been shown to be effective in other respiratory diseases such as mild upper respiratory tract infections and influenza.

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RÉSUMÉ

Les patients psychiatriques sont à risque d'hypovitaminose D et de mortalité liée au Covid-19. En plus des bénéfices sur la santé mentale, la supplémentation en vitamine D peut être potentiellement efficace pour prévenir les formes graves d'infections au Covid-19. Un dosage de vitamine D n'est pas nécessaire et n'est pas remboursé en France dans cette indication. Une supplémentation mensuelle de 50 000 UI pourrait être suffisante dans la plupart des cas. Le double de la dose est recommandé pour les patients obèses. Le risque de lithiase rénale n'est pas augmenté à ces doses, même en cas de supplémentation chez un patient sans carence en vitamine D. La crise du Covid-19 est une opportunité pour diffuser la supplémentation en vitamine D chez les patients psychiatriques, elle a en effet fait ses preuves sur d'autres pathologies respiratoires comme les infections bénignes de voies aériennes supérieures et la grippe.

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The beneficial role of vitamin D in the prevention of Covid-19 infection and severe forms has been suggested by numerous publications. After more than 12 months of viral circulation, Covid-19 (Sars-Cov-2) infected millions of people around the world, causing

hundreds of thousands of deaths, particularly among the elderly, frail and chronically ill patients. Psychiatric patients with severe mental illness are at increased risk of Covid-19 infection and of poor Covid-19 outcomes [1]. In the absence of an effective and accessible curative treatment for Covid-19 to date, the use of already existing molecules could help control the pandemic.

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1. Vitamin D as an aid in the prevention of Covid-19 infection poor outcomes

Vitamin D deficiency, defined as a circulating concentration of 25-hydroxyvitamin D, or 25(OH)D, less than 12 ng/mL (or 30 nmol/L), and vitamin D deficiency, defined as a circulating concentration of 25(OH)D between 12 and 20 ng/mL (or 50 nmol/L), can affect the immune system. Vitamin D stimulates the expression and secretion of antimicrobial peptides by monocytes/macrophages, which participates in mucosal defenses, but also stimulates the synthesis of anti-inflammatory cytokines while inhibiting the synthesis of pro-inflammatory cytokines.

Several observational studies have reported an association between low circulating concentrations of 25(OH)D and the risk of acute respiratory infections, including influenza. In addition, recent meta-analyses of randomized controlled trials report a protective effect of vitamin D supplementation on respiratory tract infections, particularly in vitamin D deficient individuals receiving daily or weekly supplementation [2].

Concerning Covid-19, the first reports show that the circulating concentration of 25(OH)D is lower in infected adults than in others [3]. In an ecological study, inverse correlations were found in 46 countries between vitamin D deficiency in the general population and the incidence of Covid-19 [4]. Specifically, the existence of vitamin D deficiency appears to precede the onset of Covid-19 infection [5], rather than vice versa.

While Covid-19 usually causes only mild symptoms, it can also progress to an uncontrolled inflammatory reaction, called a "cytokine storm", partly secondary to the negative regulation by the SARS-CoV-2 of the angiotensin converting enzyme type 2 (ACE2: a counter-regulatory enzyme that degrades angiotensin 2 to angiotensin 1-7 with antioxidant, antifibrotic and anti-inflammatory properties). The consequence is a pro-inflammatory state associated with severe tissue damage, contributing to severe forms of Covid-19 and in particular to the occurrence of acute respiratory distress syndrome, which is often fatal. The elderly and those with comorbidities such as hypertension, diabetes or obesity are at increased risk of developing a severe form of Covid-19.

Vitamin D modulates the activity of the renin-angiotensin system and the expression of ACE2 [6]. The modulation of adaptive immunity by vitamin D (stimulation of the expression of anti-inflammatory cytokines by macrophages and limitation of the production of pro-inflammatory cytokines by helper T lymphocytes type 17) could also limit the consequences of the cytokine storm.

It should also be noted that the major risk factors for vitamin D deficiency (advanced age, obesity, or chronic disease) are very similar to the risk factors for severe forms of Covid-19. In the case of Covid-19 infection, several studies have shown, taking into account potential confounding factors, that people with a low 25(OH)D concentration were more likely to progress to a severe form [7], to use non-invasive ventilation, to have a prolonged hospital stay, but also to die from Covid-19, including in intensive care units [8]. Unlike other risk factors that are mostly unmodifiable, vitamin D deficiency is very easily modifiable by simple supplementation.

The (few) published intervention studies support a beneficial effect of vitamin D supplementation in reducing the severity of symptoms in adults with Covid-19. For example, a randomized placebo-controlled clinical trial in 40 Covid-19 patients initially deficient in vitamin D showed that a greater proportion of participants who received a high dose of vitamin D (50,000 IU/d for 7 days) had no longer detectable CoV-2 SARS viral RNA at 21 days on oropharyngeal swabs compared to the placebo group (63% vs. 21% respectively; $P: 0.018$) [9]. One randomized trial reported, in 76 adults with an average age of 53 years hospitalized for Covid-19, that those who received 25(OH)D supplements in addition to standard care for Covid-19 had significantly less resuscitation

than those who received only standard care (1/50 or 2% vs 13/26 or 50%; $P < 0.001$) [10]. These results are supported by two quasi-experimental studies conducted in France during the first wave, which reported less severe forms of Covid-19 and an improvement in survival of about 90% with regular vitamin D3 supplementation in elderly people either hospitalized [11] or living in residential institutions for dependent elderly people [12]. An English study also reported that high doses of vitamin D3 (approximately 280,000 IU over a 7-day period) were associated with an 87% improvement in survival in patients hospitalized for Covid-19, regardless of baseline 25(OH)D concentrations [13]. The small numbers and design of these studies, however, justify the continuation of large randomized clinical trials.

The above data leads us to recommend the supplementation of vitamin D in psychiatric patients.

Vitamin D supplementation is a simple, effective, safe, inexpensive, and reimbursed by Health Insurance. Although there is not yet indisputable evidence that vitamin D supplementation reduces the risk of CoV-2-SARS infection, maintaining a satisfactory vitamin D status has benefits beyond Covid-19 by promoting bone and neuromuscular health, among other things, and is associated with improved prognosis in some cancers. Several national and international learned societies and expert groups have already published opinions recommending vitamin D supplementation in the context of the Covid-19 epidemic [14,15].

In the absence of any major risk associated with supplementation at the appropriate dose and given that about half of the general population in France has hypovitaminosis D [16], there is now a strong incentive to supplement psychiatric patients with vitamin D, who are by definition at risk of hypovitaminosis D. The goal is for the majority of the psychiatric population to reach a serum 25(OH)D concentration between 20 and 60 ng/mL. The most methodologically sound studies indicate that intakes of 50,000 IU vitamin D3 per month could be the most effective strategy [17]. Obese subjects should be prescribed twice this dose. This attitude corresponds in fact to the recommendation (excluding Covid-19) to maintain a satisfactory vitamin D status in the general population, and therefore does not require waiting for the results of randomized controlled trials dedicated to Covid-19 to be applied. The dosage of 25(OH)D is not necessary (and is not reimbursed in France) in this case. The fear of renal lithiasis linked to the prescription of vitamin D without prior dosage (and therefore without confirmation of vitamin D deficiency) can be reassured by the results of recent large placebo-controlled clinical trials which clearly showed that there was no increase in renal lithiasis in several tens of thousands of individuals not deficient in vitamin D (with an average 25(OH)D of around 30 ng/mL at inclusion) who had received 2000 IU/d for several years, 4000 IU/d, or 100,000 IU/month [18].

Disclosure of interest

The authors declare that they have no competing interest.

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