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Coronavirus, the immune system and vitamin D

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Summary

Vitamin D exerts extra-skeletal actions, given the presence in many different tissues of its nuclear receptors controlling transcription of genes related to autoimmune diseases and its endocrine effects mainly affecting calcium metabolism. Many papers have highlighted its ability to reduce infections and to modulate innate and adaptive cellular immunity, with an inverse correlation between the incidence of airway infections and serum vitamin D levels. During the COVID-19 epidemic, not only the elderly confined to the home, with no physical activity, minimal sun exposure and physiological reduction of the UV-radiation induced activation of vitamin D, but also people suffering from fragility fractures, often with comorbidities and treatments with bone-loss side effects (primarily steroids), as well as people in environments at high risk (such as patients and staff in hospitals), should take vitamin D supplements as an important step in the prevention of infections and their spread. In any case, randomised studies should be conducted on large populations to give value to this therapeutic strategy, given the lack of unequivocal of not univocal data on the immune supportive role of vitamin D, on the dose to be administered and blood levels to be achieved.

Key words: coronavirus, SARS-CoV2, COVID-19, vitamin D, immunity

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Introduction

The disease caused by the new coronavirus "SARS-CoV2" determines, in most cases, the onset of an inflammatory cascade characterised by a moderate release of inflammatory cytokines, sufficient to activate the immune system against the virus, and obtain remission from the disease. In some patients, on the other hand, there is a "cytokine storm", the expression of a hyper-activated immune system, which in turn is stimulated to produce other cytokines [1]. In this period the main interest of the entire medical community is focused on therapies to treat coronavirus pneumonia and its complications: in all centres drugs are used that can block the inflammatory process and the frequent vasculitis with antivirals, immunomodulators, anti-inflammatories, anticoagulants, while minimal space is left to supporting therapies such as vitamin D supplementation.
In recent years, vitamin D supplementation has been at the centre of a lively scientific debate with an exponential growth in the numbers of publications on this topic. In the PubMed database, using the search keyword "vitamin D", there is in fact a strong increase in the results retrieved, going from about 300 articles in the early 2000s to about 85,000 in 2020. This is an expression of the progressive increase in attention towards vitamin D, but also of its overprescription, a reason that made the Italian Drugs Agency (AIFA) regulate its use through "Nota 96"($), which limits its use almost exclusively to the musculoskeletal system.
There is a great deal of evidence, albeit largely observational, on the potential extra-skeletal clinical effects of vitamin D in diabetes, cardiovascular diseases and

tumours, although there is not yet the same consolidated scientific evidence of effectiveness for the musculoskeletal system. At the immune system level, significant effects have been theorised: this, in a pandemic era, is obviously of particular interest from the point of view of possible clinical-therapeutic implications. However, the evidence and also the mere observations from randomised trials are not particularly numerous and univocal in the results: going back to the PubMed research, at the time of writing this article, only 28 papers are retrieved by inserting as keywords "vitamin D" and "immune system" and only 10 with the search keys "vitamin D" and "COVID-19". The aim of the present work is to focus the relationship between vitamin D, immune system and lymphocytic populations, in order to assess the importance of its use in the current pandemic, without ignoring its proven musculoskeletal importance; especially in the elderly patient, a privileged victim of the virus and often in a condition of severe vitamin D deficiency, osteoporotic and with a history of fractures, forcibly confined at home, without carrying out physical activity and with minimal exposure to the sun.

($) Nota 96: *prevention and treatment of vitamin D deficiency in adults regardless of the determination of 25 (OH) D in institutionalized people, pregnant or lactating women, the presence of osteoporosis from any cause or osteopathies not candidates for remineralizing therapy; prevention and treatment of vitamin D deficiency in adults after the determination of 25-(OH) vitamin D with serum levels < 20 ng/mL and symptoms of hypovitaminosis (asthenia, diffuse or localized pain, frequent unmotivated falls), with the diagnosis of hyperparathyroidism secondary to hypovitaminosis D, in the presence osteoporosis of any cause or proven osteopathies candidates for remineralizing therapy.*

COVID-19 and immune system

Coronavirus disease 19 (COVID-19) is the disease caused by the new Coronavirus SARS-CoV-2, identified in China in late 2019.

The genome of Coronaviruses is made up of RNA and is protected by a protein core covered by a lipid mantle, which is associated with other proteins including the "spike" protein, which is responsible for the entry of the virus into the host cell thanks to the link with the angiotensin-converting enzyme 2 (ACE2) receptor. After entering the cells of respiratory mucous membranes, the virus releases its genetic code to initiate viral replication and consequently activate a rapid reaction of innate immunity, with the release of large amounts of cytokines, a key point in determining the extent of the infection. In the most severe cases, a violent immune response with deep lung exudate production is observed, which limits ventilation and causes widespread bilateral pneumonia. An uncontrolled inflammatory response can trigger acute respiratory distress syndrome (ARDS) and septic shock. These two complications are the main causes of hospitalisation in intensive care and mortality for COVID-19 in patients over 60 years of age with a history of smoking and comorbidity (hypertension, cardiovascular and cerebrovascular disease, and diabetes) [2].

Although the coronavirus is a respiratory pathogen, in case of an important immune response, it induces the release of an additional amount of cytokines that spreads to all organs through the circulatory system, causing multi-organ dysfunction syndrome that can cause serious damage to the kidneys, heart, intestine and brain (given the presence of the ACE2 receptor in a large number of tissues) [2].

Cytokine storms are believed to have been responsible for many casualties during the 1918 flu pandemic, the severe acute respiratory syndrome (SARS) epidemic in 2003, the H5N1 avian epidemic and the 2009 swine flu epidemic [3,4].

Both pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNFα), interleukin 1 and 6 (IL-1, IL-6), and anti-inflammatory cytokines, such as IL-6 and IL-10 antagonist receptor are elevated in the serum of patients suffering from this cytokine storm.

Following viral infection, IL-6, one of the main actors is released by different cell types (T lymphocytes and macrophages of the innate immune system); it binds its receptor IL-6R, present on the surface of various cells, triggering several inflammatory mechanisms:

- production of the vascular-endothelial growth factor (VEGF) protein by fibroblasts, with consequent response by endothelial cells of blood vessels and increased permeability of the vessels themselves;
- production of pro-inflammatory and pro-coagulant proteins in the liver;
- production of antibodies against the virus by B lymphocytes;
- activation of T helper 17 (Th17) lymphocytes, capable of eliminating virus-infected cells [5,6].

The excessive response of IL-6 can, over time, abnormally activate the immune system, with production of antibodies and T lymphocytes against self, as occurs in autoimmune diseases.

Vitamin D and the immune system

Vitamin D has a central role in physiological extra-skeletal actions due to the presence of nuclear receptors in many tissues (mainly in the prostate, colon, breast); by the control of the transcription of over 200 genes (some related to autoimmune diseases and tumours), by the endocrine effects both calciotropic (on bone, intestine and kidney) and non-calciotropic (on the pancreas, for release of insulin, and on the renin-angiotensin system); by the effects on macrophages, parathyroid and epithelial cells [7,8].

Calcitriol is also synthesised by activated macrophages, which, if in excess, could lead to hypercalcaemia as in sarcoidosis,

to modulate lymphocytic maturation induced by IL-2. This increased lymphocytic growth, linked to the contact with an "antigen-presenting cell", is associated with a hyper-production of interferon γ (IFNγ) that stimulates the formation of activated multicellular macrophages, able to produce calcitriol locally, which in turn blocks lymphocytic proliferation, with a local homeostatic mechanism [9].

Vitamin D helps to preserve "tight junctions", avoiding infiltrations of liquid and neutrophils, in fact, with junctional alterations, an increase in infections by viruses and other micro-organisms is observed [10,11].

Vitamin D improves the innate cellular immunity by reducing the severity of the cytokine storm, increasing the expression of anti-inflammatory macrophage cytokines [12] and inducing antimicrobial peptides, including human cathelicidin LL-37 and defensins. Evidence of antimicrobial activities of cathelicidins, directed against Gram-positive and Gram-negative bacteria, viruses and fungi, due to their action on their cell membranes, dates back at least twenty years ago [12,13].

Vitamin D is also a modulator of adaptive immunity and consequently helps to regenerate the endothelial tissue [14,15].

Specifically, vitamin D suppresses inflammatory responses mediated by the T helper cell type 1 (Th1) and the production of inflammatory cytokines IL-2 and IFNγ [16], promotes the cytokines produced by the T helper cell type 2 (Th2), which helps to improve the indirect suppression of Th1 [17] and promotes the induction of regulatory T cells, thus inhibiting inflammatory processes [18].

Vitamin D supplementation also increases the expression of genes with antioxidant function, determining increased production of glutathione, that saves ascorbic acid (vitamin C), which has an antimicrobial activity [19] and has therefore been proposed for the prevention and treatment of COVID-19.

As already mentioned, serum concentrations of vitamin 25(OH)-D tend to decrease with age, while mortality rates for COVID-19 increase with it. It seems reasonable to assume a correlation with lower sun exposure and reduced vitamin D production, due to lower levels of 7-dehydrocholesterol in the skin [20] and the intake of drugs that reduce vitamin D concentrations by activating the pregnane X receptor, such as antiepileptic and antineoplastic drugs, antibiotics, anti-inflammatory agents, antihypertensives, antiretrovirals, endocrine drugs and some herbal medicines [21].

Among the various scientific works that consider the ways in which vitamin D reduces the risk of viral and bacterial infections [22-26], we highlight those we believe are more significant.

Inverse correlation between the incidence of upper respiratory tract infections and serum levels of vitamin 25(OH)-D [27] has been observed: in a recent double-blind randomised clinical trial (RCT), it was observed that the administration of only 1,200 IU of vitamin D3 in school-age children ccanould reduce the risk of influenza A infection by more than 40% [28].

Martineau et al, after a meta-analysis of 25 randomised trials, pointed out level I evidence for a protective effect of 12%, provided by vitamin D supplementation against bacterial and viral infections of the respiratory tract (adjusted OR = 0.88, $p < 0.001$). These protective effects increase to 19% in subjects with a daily or weekly regimen of vitamin D, compared to those taking a monthly bolus of vitamin D (adjusted OR = 0.81, $p < 0.001$) and reach 70% in subjects with serum levels < 25 nmol/l, resident at northern latitudes and corrected by supplementation (adjusted OR = 0.30, $p = 0.006$) [29]. Grant et al. pointed out a discrepancy in results between observational studies, which showed that vitamin D supplementation reduced the risk of disease, and RCTs that did not confirm this [30-34]: they concluded that the discrepancy could be attributable to several factors, including the recruitment of participants with relatively high vitamin D blood levels, administration of low doses, failure to measure basal levels and the achievement of different peak values [35]. A comprehensive review of this issue in 2018 concluded that vitamin D should reduce the risk of influenza, but that further studies are needed [36].

What dose of vitamin D?

People at risk of influenza and/or COVID-19 should consider taking 10,000 IU/day of vitamin 25(OH)-D for 1 month, followed by a maintenance dose of 5,000 IU/day for 24 weeks, with the aim of achieving concentrations of 40-60 ng/ml (100-150 nmol/l) [37,38].

In a recent review, a reduction in the severity of COVID-19 infection was observed with 200,000-300,000 IU of vitamin 25(OH)-D, taken in fractional doses of 50,000 IU [39].

Given the long period of time that we will have to live with the virus, after the first months of treatment with vitamin 25(OH)-D, we suggest to continue with a monthly administration of 0.266 mg of calcifediol and to assess both the blood levels vitamin D, in order to regulate the dosage, and metabolic markers of the bone as for any patient undergoing treatment for osteoporosis. For treatment of people with COVID-19, even higher doses of vitamin D3 may be useful [33]. Moreover, there is evidence today that prolonged supplementation of vitamin D3 with doses of 100 mcg (4000 IU)/day is safe [40].

Concerning prolonged treatment with vitamin D, the literature recommends that single doses should not exceed 100,000 IU, because with higher doses an increase in bone resorption indexes and a paradoxical increase in falls and fractures have been observed [41]. However, it has been shown that toxicity from excessive amounts of vitamin D, taken at inappropriate doses, is very rare and not dangerous for the health of patients, in accordance with our observations in patients who have made important mistakes when taking preparations.

Another therapeutic hypothesis could be the association with magnesium, which collaborates in the activation of vitamin D and contributes directly to calcium and phosphate homeostasis.

Finally, an aspect not to be neglected is a correct diet, with at least 1000-1500 mg/day of calcium [42,43], especially in the elder-

ly who present frequent malabsorption and reduced intake of dairy products for an increasingly common lactose intolerance with secondary hyperparathyroidism and calcium homeostasis alteration. In addition, vitamin D has demonstrated better efficacy in the presence of adequate calcium intake.

In this period of health emergency, we have reduced but not interrupted contact with patients who come to our bone metabolism clinic. Using e-mail and telephone contact (not having had the authorisation required to interact with telemedicine), we were able to check periodic blood chemistry tests and renew treatment plans (although their expiration date was extended) of about 50 patients, to whom we have recommended a doubling of the dose of vitamin D for 3 months, without ever exceeding 100,000 IU per administration, with the purpose of achieving a blood level of 50-60 ng/ml, often with advice to dose the makers of bone metabolism after that period.

Conclusions

During the COVID-19 epidemic, not only the elderly, forced to live a sedentary life at home, but also those who frequent at-risk environments such as hospitals (patients and staff), should consider a vitamin D supplement as an important aid for prevention and spread of the virus.

However, the elderly, characterised by osteoporotic bone, often suffering from fragility fractures, being sarcopenic, with reduced intake and intestinal absorption of calcium, are those at highest risk due to the lack of the basic mechanical stimulus for the bone (i.e. weight bearing) and minimal exposure to the sun, aggravated by the physiological reduction of synthesis of vitamin D by the skin.

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