

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23

## VITAMIN D SUPPLEMENTATION AS A RATIONAL PHARMACOLOGICAL APPROACH IN THE COVID-19 PANDEMIC

León FERDER<sup>1</sup>, Virna Margarita MARTÍN GIMÉNEZ<sup>2</sup>, Felipe INSERRA<sup>1</sup>, Carlos TAJER<sup>3</sup>, Laura ANTONIETTI<sup>3,4</sup>, Javier MARIANI<sup>3</sup>, Walter MANUCHA<sup>5,6\*</sup>

- 1- Maimónides University, Buenos Aires, Argentina.
- 2- Institute of Research in Chemical Sciences, School of Chemical and Technological Sciences, Cuyo Catholic University, San Juan, Argentina.
- 3- Department of Cardiology, Hospital El Cruce Néstor C. Kirchner, Av. Calchaquí 5401, Florencio Varela, Buenos Aires, Argentina, 1888.
- 4- Arturo Jauretche National University. Av. Calchaquí 6200, Florencio Varela, Buenos Aires, Argentina, 1888.
- 5- Pathology Department, Pharmacology Area, Medical Sciences College, National University of Cuyo, Mendoza, CP5500, Argentina.
- 6- National Scientific and Technical Research Council, Institute of Medical and Experimental Biology of Cuyo (IMBECU, CONICET), Mendoza, Argentina.

\* Corresponding author: Walter MANUCHA, Ph.D.

Área de Farmacología, Departamento de Patología, Facultad de Ciencias Médicas, Universidad Nacional de Cuyo. Fax: 54-0261-4287370. Telephone: 54-261-4135000, ext. 2739.

E-mail: [wmanucha@yahoo.com.ar](mailto:wmanucha@yahoo.com.ar)

24 **Abstract**

25 The COVID-19 pandemic has reached most of the countries worldwide causing death, which often  
26 results from an inflammatory storm associated with severe acute respiratory syndrome (SARS). This  
27 has prompted researchers to seek specific novel and definitive treatments urgently. In this context, it is  
28 interesting to evaluate the preventive and therapeutic effects of existing pharmacological agents that  
29 could be useful. In this regard, vitamin D supplementation, particularly in individuals likely to be  
30 deficient, may be a promising option. Vitamin D is a hormone that modulates many of the same  
31 inflammatory and oxidative signaling pathways triggered during COVID-19. For example, vitamin D  
32 suppresses the actions of the renin-angiotensin system, which has a determining role in the  
33 pathophysiology of the inflammatory response related to COVID-19. This paper analyzes the evidence  
34 that vitamin D supplementation might be a valuable preventive/therapeutic measure in groups at risk of  
35 or infected with COVID-19. It also discusses how clinical studies could be best designed to evaluate  
36 the possible advantages of vitamin D supplementation for the benefit of public health during the  
37 pandemic.

38

39

40

41

42

43

44

45

46 **Keywords**

47 COVID-19; vitamin D; inflammation; oxidative stress; renin-angiotensin system; prevention/treatment

## 48 **Introduction**

49 At present, multiple therapeutic strategies are being frantically sought to address the COVID-19 crisis.  
50 Among the most prominent approaches are the development of vaccines, anti-retroviral drugs,  
51 corticosteroids, and immunomodulatory drugs. Due to the urgency of the epidemic outbreak and the  
52 lack of sufficient experience with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),  
53 some empirical treatments for COVID-19 are also proposed on a rational basis. More specifically,  
54 randomized controlled trials (RCTs) are lacking that support the benefit of vitamin D supplementation  
55 in the population and/or patients exposed to SARS-CoV-2. However, an ever-growing number of  
56 findings are strengthening and validating such claim.

57 The system that integrates vitamin D has an ancestral origin that involves it with a primordial defense  
58 system. Vitamin D receptors (VDRs) were present in very primitive organisms that lacked skin, bones,  
59 cardiovascular systems, kidneys, and even lungs (20) indicating that the purpose must have been other  
60 than that conventionally known for vitamin D. More recently, VDRs were described in the cytoplasm,  
61 nuclear membrane, and even organelles such as mitochondria (21, 58). The genomic and non-genomic  
62 effects of vitamin D are ultimately the result of hormone-receptor binding that, after translocating to  
63 the nucleus, modulates the expression of genes involved in phospho-calcium metabolism (36, 45). At  
64 the same time, a considerable number of "non-classical" vitamin D actions have been described,  
65 including the inhibition of cell proliferation, secretion of other hormones, suppression of T-cell  
66 proliferation, and modulation of cytokines (14). Thus, vitamin D and its metabolites have been shown  
67 to participate actively in the regulation of innate and adaptive immune responses. Consequently, its  
68 deficiency is associated with a series of infections, as well as autoimmune and allergic conditions (67).  
69 These data reinforce the original notion that the VDR-metabolite system would fulfill a central role in  
70 cellular and tissue defense through immune mechanisms and/or regulation of inflammatory processes.  
71 Furthermore, vitamin D would regulate the expression of 0.5 to 5% of the total human genome, which  
72 amounts to approximately 100 to 1,250 genes. Therefore, it is not surprising that vitamin D interacts  
73 with multiple genes commonly expressed in humans, such as those related to the renin-angiotensin-  
74 aldosterone system (RAAS), among others (28).

75

76

## 77 **Link between vitamin D/RAAS and COVID-19**

78 Apart from the immune system, evolution enabled vitamin D to interact with other fundamental  
79 systems in the maintenance of cellular homeostasis, such as the RAAS. As previously described in  
80 Figure 1 (20), Vitamin D opposes or modulates RAAS signaling pathways. RAAS regulates body  
81 hydroelectrolyte composition and hemodynamics. Of central interest for the present perspective, it also  
82 functions as a complex pro-inflammatory system (20). Consequently, most mammalian cells express  
83 both VDR and different RAAS receptors. Vitamin D, its metabolites, and receptors, on the one hand,  
84 and RAAS molecules and its receptors, on the other, are part of a delicate cellular/tissue defense  
85 system mediating pro- and anti-inflammatory processes.

86 Additionally, there are some close connections between COVID-19 and the RAAS, since serum  
87 angiotensin II (Ang II) levels in infected patients were significantly elevated and directly proportional  
88 to the viral load and lung damage observed (35). SARS-CoV-2 has been shown to bind to angiotensin-  
89 converting enzyme 2 (ACE2) receptors to invade human lung epithelial cells and initiate the infection.  
90 At the same time, ACE2 produces anti-inflammatory, antioxidant, anti-fibrotic, and anti-hyperplasia  
91 effects. This leads to the degradation of Ang II at the lung level through the ACE2/Ang1-7/Mas  
92 receptor signaling pathway, i.e., the counter-regulatory RAAS axis with opposite actions to the  
93 classical RAAS axis (ACE/Ang II/AT1 receptor pathway). The increase in the degradation of Ang II  
94 prevents its toxic over-accumulation, which would cause the acute respiratory distress syndrome often  
95 present in COVID-19 (13, 18, 59, 69). Independently of COVID-19, RAAS is also involved in the  
96 regulation of lung tissue proliferation, inflammation, and fibrosis in several pulmonary pathologies,  
97 such as acute lung injury, asthma, pulmonary arterial hypertension, chronic obstructive pulmonary  
98 disease, and idiopathic pulmonary fibrosis, among others (62).

99 Concerning vitamin D/RAAS interaction, the participation of the ACE2/Ang(1-7)/MasR signaling  
100 pathway has been recently demonstrated in hypertensive rats (17). In humans, vitamin D was found to  
101 act as a cofactor in the attenuation of incident atrial fibrillation by RAAS inhibition (68). Additionally,  
102 exacerbated RAAS activation at the hepatic level causes liver dysfunction and increases the risk of  
103 developing diabetes mellitus. In this regard, calcitriol was shown to modulate the altered upregulation  
104 of liver RAAS under conditions of insulin resistance in mice (33). Vitamin D is a potent suppressor of  
105 renin production (Figure 1) (20). Thus, low plasma levels of vitamin D are associated with an increase  
106 in renin synthesis, which results in over-activation of RAAS and increased production of Ang II, and

107 vice versa (34, 55). It has been demonstrated that vitamin D deficiency also results in overexpression  
108 of angiotensin-converting enzymes (ACE and ACE2) (73). Furthermore, in patients with D  
109 hypovitaminosis, the re-establishment of normal vitamin D levels causes blockade of peripheral RAAS  
110 (9).

111 In vitamin D receptor-null mice, the development of induced acute lung injury was found to be more  
112 severe than in wild-type mice, together with increased levels of pulmonary Ang II and renin.  
113 Pretreatment of vitamin D receptor-null mice with losartan reduced the severity of pulmonary injury  
114 indicating that vitamin D, via its receptors, attenuates acute lung injury by blocking RAAS (30).  
115 Additionally, Xu et al. showed that calcitriol inhibits ACE and induces ACE2 expression in rat lung  
116 while reducing Ang II levels and inhibiting AT1R expression. The authors suggest that VDR  
117 activation may exert protective effects on LPS-induced lung injury by regulating the balance between  
118 RAAS members (73). Moreover, if vitamin D deficiency is chronic, the uncontrolled RAAS over-  
119 activation for extended periods may induce pulmonary fibrosis through the exacerbated and  
120 accelerated increase in extracellular matrix deposition in lung tissues (56).

121 Lung epithelial cells exhibit a high expression of enzyme 1  $\alpha$ -hydroxylase allowing for the local  
122 synthesis of 1,25-dihydroxyvitamin D -the most active form of vitamin D- also called calcitriol.  
123 Calcitriol inhibits the production and secretion of many cytokines from bronchial smooth muscle cells,  
124 such as platelet-derived growth factor, RANTES (regulator in the activation of expressed and secreted  
125 normal T cells), and matrix metalloproteinases, leading to reduced proliferation and inflammation in  
126 lung smooth muscle cells. Vitamin D stimulates the synthesis of interleukin 10 by CD4<sup>+</sup> CD25<sup>+</sup>  
127 Foxp3<sup>+</sup> and T-regulatory cells. At the same time, it inhibits the activation of dendritic cells by  
128 downregulating the expression of CD80/86 and CD40. Furthermore, vitamin D stimulates the  
129 expression of cathelicidin and many other anti-infective molecules (12, 15, 54).

130 Supplementation with 1,25-dihydroxyvitamin D suppresses the recruitment of eosinophils and  
131 lymphocytes into the airways, decreases IL-4 production of T cells, and inhibits T cell migration by  
132 attenuating the inflammatory response (66). It also works as an adjuvant for other therapies, such as  
133 immunotherapy against allergens (60). Simultaneous administration of vitamin D and dexamethasone  
134 in steroid-resistant asthmatic patients increased IL-10 synthesis to levels similar to those found in  
135 steroid-sensitive patients treated with dexamethasone alone (74).

136 In a rat model of asthma, vitamin D treatment significantly reduced serum IgE and eotaxin levels (65).  
137 Additionally, it decreased the infiltration of inflammatory cells in the airways, serum levels of IL-6,  
138 tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), and IL-1 $\beta$ , as well as the expression of the apoptotic protein  
139 associated with Bcl 2, caspase-3, TLR4, nuclear factor kappa B (NF- $\kappa$ B), and phosphorylated p65 NF-  
140  $\kappa$ B. As a result, vitamin D raised serum levels of IL-10 reducing the inflammatory and apoptotic  
141 response in this rat model of asthma (77). Importantly, vitamin D suppressed the synthesis of 8-  
142 isoprostane (8-iso), IL-6, and granulocyte-macrophage colony-stimulating factors in human bronchial  
143 epithelial cells exposed to contaminating particles. Vitamin D also increased the expression of genes of  
144 the G6PD antioxidant pathway and the levels of oxidized glutathione. Therefore, vitamin D seems to  
145 protect the lungs and airways of asthma patients through its anti-inflammatory and antioxidant effects  
146 (46). (Figure 2)

147 In the murine model of bleomycin-induced lung inflammation, calcitriol reduced early lung  
148 inflammation by attenuating immune cell infiltration, suppressing the secretion of inflammatory  
149 cytokines, blocking translocation of NF- $\kappa$ B p65, inhibiting phosphorylation of lung p38 MAPK and  
150 protein kinase B (Akt). It also attenuated the expression of smooth muscle alpha-actin (a marker for  
151 epithelial-mesenchymal transition in the lungs, which promotes fibrosis) while decreasing the  
152 phosphorylation of Smad and the up-regulation of transforming growth factor-beta 1 (TGF- $\beta$ 1) (63). In  
153 addition, calcitriol caused a 40% reduction in the recruitment of neutrophils to the lungs in an animal  
154 model of acute lung injury. The anti-inflammatory effect of vitamin D may be mediated by the  
155 inhibition of IL-8 secretion at the lung level (61).

156 Administration of vitamin D to neonatal rats exhibiting hyperoxia-induced lung injury (as a model of  
157 bronchopulmonary dysplasia) attenuated lung injury through various protective actions, such as  
158 preserving the integrity of lung structure, decreasing inflammation by negatively regulating TLR4  
159 activation, and reducing extracellular matrix deposition and the inhibition of lung cell apoptosis (75).  
160 Vitamin D was also shown to have immunomodulatory and anti-inflammatory effects in the treatment  
161 of cystic fibrosis of the airways, as it reduces the expression of CD279 (PD-1) in CD4<sup>+</sup> and CD8<sup>+</sup> T  
162 cells. Furthermore, vitamin D decreases the frequency of CD8<sup>+</sup> T and invariant mucosa-associated T  
163 cells that co-express activation markers for CD38 and D antigen in human leukocytes. Therefore,  
164 vitamin D treatment would prevent the progression of lung damage associated with cystic fibrosis of  
165 the airways (49). (Figure 2)

## 166 **Vitamin D lung-protection: A rational approach to COVID-19**

167 Oxidative stress caused by tobacco smoke is known to worsen the progression of chronic obstructive  
168 pulmonary disease (COPD). In this sense, vitamin D has also been proposed as a natural anti-  
169 inflammatory and antioxidant capable of improving the prognosis of this pulmonary pathology in  
170 smokers (6). COPD patients were shown to have lower plasma vitamin D levels than healthy patients,  
171 suggesting a possible correlation between weak antioxidant defense and the development of this lung  
172 disease (1). In this respect, a few years ago, our group raised the discussion about a worldwide  
173 pandemic of vitamin D deficiency as a possible explanation for the high cellular inflammatory activity  
174 induced by RAAS (20). The original discussion involved a significant number of pathologies, mainly  
175 cardiovascular, although all of them with a similar inflammatory basis. Currently, with the main focus  
176 on acute lung inflammation caused by COVID-19, the Irish Longitudinal Study on Aging (TILDA  
177 2020) reinforces the idea that adequate vitamin D supplementation, especially in older people, may be  
178 beneficial for the vulnerable population during the COVID-19 outbreak (31).

179 In summary, the anti-inflammatory, antioxidant, and antiviral properties of vitamin D, in addition to its  
180 ability to modulate RAAS, make it an attractive strategy for preventing COVID-19 and its associated  
181 organic damage (5). (Figure 2)

182

## 183 **Promising results according to vitamin D levels and supplementation**

184 An increasing number of papers, including systematic reviews and meta-analyses, confirm the link  
185 between a higher incidence of severe COVID-19, including death, and low serum levels of vitamin D.  
186 Remarkably, serum vitamin D concentration was inversely associated with the risk and severity of  
187 acute respiratory tract infection (47). A fundamental analysis of the link between vitamin D deficiency  
188 and its treatment, associated with the incidence of COVID-19, was performed by Meltzer and  
189 colleagues using data from the electronic health record at the University of Chicago Medicine. The  
190 main result of this analysis is the comparison of patients with a low measured basal level of vitamin D  
191 and no supplementation treatment versus patients with a low basal level of vitamin D but  
192 supplemented with this vitamin. The non-supplemented group showed a significantly higher number of  
193 positive tests for COVID-19. Among the treated patients, the vitamin D protective effect against the  
194 SAR-CoV-2 virus infection was significant only in the group with basal vitamin D-deficiency (40).

195 Additionally, there is robust information showing that as vitamin D levels increase, the number and  
196 severity of respiratory infections decrease (70, 76). Several studies that evaluated the role of vitamin D  
197 in respiratory viral infections, using different methodologies and dosages and comparing vitamin D  
198 supplementation vs. placebo, have mostly found a positive effect for vitamin D (4, 26). Although the  
199 mechanisms are not fully understood, the combined improvements in the immunomodulatory and anti-  
200 inflammatory response, together with the proven germicidal effects of vitamin D, take part in its  
201 protective effects. This background provides the medical community with enough support to  
202 investigate whether vitamin D effects are also beneficial in the context of COVID-19.

203 Different strategies are available to increase vitamin D levels: Food fortification programs, increasing  
204 sun exposure by stimulating outdoor activities, and vitamin D supplementation, among others. Both  
205 vitamin D food fortification and sun exposure are useful to improve low serum levels of vitamin D. It  
206 is evident that this strategy enhances human defense against viral and bacterial infection. Vitamin D  
207 food fortification represents both a feasible and recommended measure, whose implementation as a  
208 health policy was suggested in a recent review, taking as a guide the program used in Finland. The  
209 related legislation, however, must be generated by each of the interested countries (48). Both historical  
210 and recent evidence on the mechanisms of sun-dependent vitamin D production and its protective  
211 effects were reviewed by Wacker and Holick (71). It is worth noting that the cutaneous production of  
212 vitamin D depends on many variables. The lower rates of skin vitamin D production occur among  
213 individuals with darker skin or reduced sun exposure, subjects living in higher latitudes in winter,  
214 nursing home residents, or elderly people. Accordingly, COVID-19 is more prevalent among African  
215 Americans, individuals living in northern cities in late winter, and older adults, all of whom have an  
216 increased risk of vitamin D deficiency (39). As shown in a recent systematic review and meta-analysis  
217 (42), vitamin D supplementation is superior to sunbathing at elevating vitamin D serum levels.  
218 However, increasing sun exposure or improving the general health condition of the population at high  
219 risk of vitamin D deficiency described above is not easy to achieve. This explains the key role of  
220 vitamin D supplementation. Notwithstanding this, a balanced and healthy diet that includes foods with  
221 high vitamin D content, along with an exercise routine, preferably outdoors, aimed at reducing or at  
222 least maintaining body weight and improving aerobic capacity are essential preventive strategies to  
223 enhance the defenses against SARS-CoV-2 (41).

224 Recently, Grant and colleagues suggested that vitamin D supplementation could reduce the risk of  
225 influenza and COVID-19 infections (24). This conclusion is in line with the existence of abundant data



226 in support of the protective action of vitamin D in multiple inflammatory and oxidative pulmonary  
227 diseases, such as that caused by SARS-CoV-2. Grant et al. showed that the degree of protection  
228 against influenza and COVID-19 increases as vitamin D levels increase. However, the results have not  
229 allowed establishing an adequate cut point level yet. Nonetheless, an observational study reported that  
230 38 ng vitamin D/mL is an appropriate serum value to decrease the risk of acute viral respiratory  
231 infections (53). Additionally, some authors suggest maintaining a serum vitamin D level of at least 30  
232 ng/mL or even within a range of between 40-60 ng/mL to reduce infectious processes. Thus, it has  
233 been reported that post-surgical hospital infections are three times higher when vitamin D values are  
234 lower than 30 ng/mL (51), and that these types of infections were reduced by 33% for every 10 ng/mL  
235 of increase in serum vitamin D (32) levels.

236 Following medical evidence, frequent clinical behavior suggests that in the face of severe vitamin D  
237 deficiency, a two-stage therapeutic scheme should be established. The first stage consists of a high  
238 loading dose followed by a lower maintenance dose. In this regard, the use of the so-called "loading  
239 dose" of vitamin D has been reported to achieve a target plasma level of 30 ng/mL vitamin D by using  
240 different dosage regimens (daily, weekly, biweekly, and monthly). Remarkably, in patients with  
241 elevated inflammatory markers -such as obese subjects- the necessary supplementation should be two  
242 to threefold higher than that established for the general population. In the case of overweight patients,  
243 such supplementation should be at least 1.5 times higher than the general population (19).

244 Even though knowledge about the role of vitamin D is still scarce, pooled data support its role as an  
245 adjuvant strategy aimed at providing rapid and effective protection against the risk of infection by  
246 SARS-CoV-2. In this scenario, different approaches have been tried, such as daily vitamin D doses for  
247 a short time or the use of an initial loading dose followed by high vitamin D doses for a short time. In  
248 each case, and in times of pandemic, this allows achieving plasma concentrations within appropriate  
249 ranges of 30-50 ng/mL or higher. More specifically, strategies such as that suggested by Grant et al.  
250 propose a dose of 10,000 IU/day for a month to quickly reach the goal of 40-60 ng vitamin D/mL,  
251 followed by 5,000 IU/day for a few more weeks (23).

252 The proposed level of high vitamin D doses is striking, neglecting its possible toxic effects; however,  
253 in this respect, some studies show that a dose of 10,000 IU/day for 4-6 months has no adverse effects.  
254 Amir et al. verified no toxic effects in Canadian women with breast cancer and bone metastases (2).  
255 Similarly, the research team led by Dr. Holick -one of the most prominent groups in vitamin D studies-

256 supplemented cancer patients with high doses of vitamin D finding no toxicity; on the contrary, it  
257 improved the intestinal microbiota of treated patients (11). The same group worked with 10,000  
258 IU/day for 6 months without causing hypercalcemia and achieving vitamin D levels of the order of  
259  $78.6 \pm 13$  ng/mL (57). Another study treated psychiatric patients with doses of 5,000 or 50,000 IU/day  
260 for 16 months without adverse effects. The only caveat was that if a patient also received calcium  
261 supplementation, the dose should not be high to minimize the risk of hypercalcemia (38). The bet was  
262 higher in other works with proposals for an initial dose of 100,000 IU to achieve serum concentrations  
263 above 20 ng/mL, an initial dose of 300,000 IU for levels above 30 ng/mL, and even an initial dose of  
264 500,000 IU for healthy adults (16, 29). In another clinical trial, a monthly dose of 100,000 IU  
265 increased neither the incidence rate of kidney stone events nor of hypercalcemia (37).

266 Current information is controversial regarding what should be the supplemental dose of vitamin D to  
267 be administered to patients. Age, diet, weight, sun exposure, and concomitant diseases may have  
268 clinical relevance because they may change the requirements and production capacity. Consider the  
269 dose of vitamin D needed to attain its bone action; the maximum dose suggested for this purpose is  
270 4,000 IU daily. Nevertheless, the optimal serum level needed to protect our body against infections  
271 remains unclear. In this sense, serum levels of 50 to 60 ng vitamin D/mL seem to be adequate. With  
272 11,000 IU vitamin D/day, it takes about four weeks to achieve the above serum levels, and with 4,000  
273 IU vitamin D/day, it takes over 12 weeks. The proposed higher dose is not associated with an  
274 increased risk of toxicity. In a recently published Consensus, it was suggested that doses ranging from  
275 4,000 IU (for bone action) to 10,000 IU (for non-calcemic effects) are safe and effective to achieve the  
276 advantageous effects of vitamin D (22, 23, 27). However, additional studies are required to confirm  
277 what is the best protection threshold against COVID-19 or to treat recently infected patients (10).

278 Based on scarce information comparing a high single dose versus daily doses of vitamin D, some  
279 authors have expressed concern about data that show better results with daily doses of vitamin D.  
280 However, it is interesting to note that the endpoint evaluated in this randomized study was not  
281 infectious diseases (3). Additionally, in a recent publication of a randomized trial, 120 children with a  
282 confirmed diagnosis of sepsis were assigned to receive either a single dose of 150,000 IU of vitamin  
283 D<sub>3</sub> or a placebo. SOFA score and the percentage of children with septic shock were lower in the  
284 vitamin D group (72).

285 Finally, latest reports have proposed that vitamin D supplementation could improve the clinical course  
286 of patients infected with SARS-CoV-2 (8, 43). The same recommendation was reinforced by Grant  
287 and colleagues, who suggested that vitamin D supplementation, could reduce the risk of COVID-19  
288 (24).

289

## 290 **Conclusion and prospects**

291 To sum up, and in the face of this devastating epidemic for which we still lack effective treatments, the  
292 present perspective proposes to explore the potentially protective effect of high doses of vitamin D to  
293 increase blood and tissue levels rapidly. This approach intends to counteract RAAS overload, thus  
294 improving the course of COVID-19 and its respiratory complications, even protecting other organs.  
295 The purpose is to open the discussion and create an appropriate debate on the prospect of prescribing  
296 vitamin D to the general population -particularly the most vulnerable- as well as achieving a serum and  
297 tissue vitamin D level to counteract the imbalance of some RAAS and manifest its anti-inflammatory  
298 effects.

299 We believe that this strategy applied at the population level could provide an additional tool for the  
300 defense against the SARS-CoV-2 virus without adverse effects, as demonstrated in the review of more  
301 than 76,000 patients included in controlled trials with vitamin D supplementation. A possible dose to  
302 obtain rapid increases in plasma vitamin D levels could range between 5,000 IU and/or 10,000 IU  
303 daily, or 50,000 IU to 100,000 IU weekly (7). Given the tentativeness of the proposed dose, the use of  
304 lower doses could be considered in children or young adults with low exposure risk to the virus. In this  
305 regard, our working group is advancing in the development of controlled protocols with different  
306 populations of people at risk or already infected, evaluating physiological parameters and clinical  
307 events. Even though said intervention does not intend to eliminate the virus, its potential is promising  
308 to hinder viral entry and/or improve patient evolution. That is, vitamin D intake could improve the  
309 health of the patients so that they can be in better shape to face COVID-19 and boost their defenses  
310 against this infection, or even against other equivalent diseases. Furthermore, it should be borne in  
311 mind that quarantine, as a protection strategy for the population against infection, complicates the  
312 defense mechanisms due to a significant decline in serum vitamin D levels by reduced sun exposure.

313 As previously described, we consider that the present recommendation finds support in multiple  
314 reports. Accordingly, Grant and colleagues recently proposed to raise serum vitamin D concentrations  
315 through supplementation claiming that this strategy could reduce the incidence, severity, and risk of  
316 death from influenza, pneumonia, and the current COVID- 19 epidemic (25). Additionally, Panarese  
317 and Shahini proposed the prophylactic use of usual vitamin D doses to mitigate the aggressive  
318 progression of the disease in Europe (44). In turn, Rhodes and collaborators have proposed vitamin D  
319 supplementation, at least for people in the northern hemisphere who are at higher risk of severe illness  
320 and death (52). The same is recommended by the United Kingdom Association of Dietitians (64).

321 Finally, ten RCTs around the world (50), including one by our group (# NCT04411446), are currently  
322 investigating whether supplementation with vitamin D could be an effective strategy against viral  
323 complications. Such trials aim to validate this hypothesis for the benefit of public health, particularly  
324 in the context of the COVID-19 crisis.

325

## 326 **Funding**

327 This work was supported by grants from the Research and Technology Council of Cuyo University  
328 (SECyT), Mendoza, Argentina, and from ANPCyT FONCyT, both of which were awarded to Walter  
329 Manucha. Grant no. PICT 2016-4541, and IP-COVID-19-931.

## 330 **Declaration of conflicting interest**

331 The author(s) declare no potential conflicts of interest concerning the research, authorship, and/or  
332 publication of this article.

## 333 **Acknowledgments**

334 The authors are grateful to Elena M.V. de Cavanagh, Ph.D. - Instituto Massone SA, Arias 3751 -  
335 (C1430CRC), Buenos Aires, Argentina, (+54 9 11) 45656910, for critical reading of the manuscript.

336

337

338 **References**

- 339 1. **Al-Azzawi MA, Ghoneim AH, Elmadbouh I.** Evaluation of Vitamin D, Vitamin D Binding  
340 Protein Gene Polymorphism with Oxidant - Antioxidant Profiles in Chronic Obstructive Pulmonary  
341 Disease. *J Med Biochem* 36: 331-340, 2017.
- 342 2. **Amir E, Simmons CE, Freedman OC, Dranitsaris G, Cole DE, Vieth R, Ooi WS, Clemons M.**  
343 A phase 2 trial exploring the effects of high-dose (10,000 IU/day) vitamin D(3) in breast cancer  
344 patients with bone metastases. *Cancer* 116: 284-291, 2010.
- 345 3. **Apaydin M, Can AG, Kizilgul M, Beysel S, Kan S, Caliskan M, Demirci T, Ozcelik**  
346 **O, Ozbek M, Cakal E.** The effects of single high-dose or daily low-dosage oral cholecalciferol  
347 treatment on vitamin D levels and muscle strength in postmenopausal women. *BMC Endocr*  
348 *Disord* 18(1): 48, 2018.
- 349 4. **Arihiro S, Nakashima A, Matsuoka M, Suto S, Uchiyama K, Kato T, Mitobe J, Komoike N,**  
350 **Itagaki M, Miyakawa Y, Koido S, Hokari A, Saruta M, Tajiri H, Matsuura T, Urashima M.**  
351 Randomized trial of vitamin D supplementation to prevent seasonal influenza and upper respiratory  
352 infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 25: 1088-1095, 2019.
- 353 5. **Aygun H.** Vitamin D can prevent COVID-19 infection-induced multiple organ damage. *Naunyn*  
354 *Schmiedebergs Arch Pharmacol* 1-4, 2020.
- 355 6. **Biswas S, Hwang JW, Kirkham PA, Rahman I.** Pharmacological and dietary antioxidant  
356 therapies for chronic obstructive pulmonary disease. *Curr Med Chem* 20: 1496-530, 2013.
- 357 7. **Bolland M, Grey A, Gamble G, Reid I.** The effect of vitamin D supplementation on skeletal,  
358 vascular, or cancer outcomes: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol* 2: 307-20,  
359 2014.
- 360 8. **Carpagnano GE, Di Lecce V, Quaranta VN, Zito A, Buonamico E, Capozza E, Palumbo A, Di**  
361 **Gioia G, Valerio VN, Resta O.** Vitamin D deficiency as a predictor of poor prognosis in patients with  
362 acute respiratory failure due to COVID-19. *J Endocrinol Invest.* 1-7, 2020. doi:10.1007/s40618-020-  
363 01370-x

- 364 9. **Carrara D, Bruno RM, Bacca A, Taddei S, Duranti E, Ghiadoni L, Bernini G.** Cholecalciferol  
365 treatment downregulates renin-angiotensin system and improves endothelial function in essential  
366 hypertensive patients with hypovitaminosis D. *J Hypertens* 34: 2199–2205, 2016.
- 367 10. **Chakhtoura M, Napoli N, El Hajj Fuleihan G.** Commentary: Myths and facts on vitamin D  
368 amidst the COVID-19 pandemic. *Metabolism* 109: 154276, 2020. doi:10.1016/j.metabol.2020.154276.
- 369 11. **Charoenngam N, Shirvani A, Kalajian TA, Song A, Holick MF.** The Effect of Various Doses of  
370 Oral Vitamin D3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-  
371 blinded, Dose-response Study. *Anticancer Res* 40: 551-556, 2020.
- 372 12. **Chen WW, Cai XX, Tian WM, Shang YX.** Expression of RANTES in the lung tissue of  
373 asthmatic rats, and the intervention effect of vitamin D on RANTES expression. *Zhongguo Dang Dai*  
374 *Er Ke Za Zhi* 14: 863-868, 2012.
- 375 13. **Cheng H, Wang Y, Wang GQ.** Organ-protective effect of angiotensin-converting enzyme 2 and  
376 its effect on the prognosis of COVID-19. *J Med Virol* 92(7): 726-730, 2020.
- 377 14. **Christakos S, Raval-Pandya M, Wernyj RP, Yang W.** Genomic mechanisms involved in the  
378 pleiotropic actions of 1,25-dihydroxyvitamin D3. *Biochem J* 316 ( Pt 2): 361-71, 1996.
- 379 15. **Chung C, Silwal P, Kim I, Modlin RL, Jo EK.** Vitamin D-Cathelicidin Axis: at the Crossroads  
380 between Protective Immunity and Pathological Inflammation during Infection. *Immune Netw* 20(2):  
381 e12, 2020. doi:10.4110/in.2020.20.e12.
- 382 16. **Cipriani A, Romagnoli E, Scillitani A, Chiodini I, Clerico R, Carnevale V, Mascia ML,**  
383 **Battista C, Viti R, Pileri M, Eller-Vainicher C, Minisola S.** Effect of a Single Oral Dose of 600,000  
384 IU of Cholecalciferol on Serum Calcitropic Hormones in Young Subjects With Vitamin D  
385 Deficiency: A Prospective Intervention Study. *J Clin Endocrinol Metab* 95: 4771-4777, 2010.
- 386 17. **Cui C, Xu P, Li G, Qiao Y, Han W, Geng C, Liao D, Yang M, Chen D, Jiang P.** Vitamin D  
387 receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive  
388 rats and angiotensin II-exposed microglial cells: Role of renin-angiotensin system. *Redox Biol* 26:  
389 101295, 2019. <https://doi.org/10.1016/j.redox.2019.101295>.

- 390 18. **Danser AHJ, Epstein M, Batlle D.** Renin-Angiotensin System Blockers and the COVID-19  
391 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System  
392 Blockers. *Hypertension* 75(6): 1382-1385, 2020.
- 393 19. **Ekwaru JP, Zwicker JD, Holick MF, Giovannucci E, Veugelers PJ.** The importance of body  
394 weight for the dose response relationship of oral vitamin D supplementation and serum 25-  
395 hydroxyvitamin D in healthy volunteers. *PLoS One* 9: e111265, 2014.  
396 doi:10.1371/journal.pone.0111265.
- 397 20. **Ferder M, Inserra F, Manucha W, Ferder L.** The world pandemic of vitamin D deficiency  
398 could possibly be explained by cellular inflammatory response activity induced by the renin-  
399 angiotensin system. *Am J Physiol Cell Physiol* 304(11): C1027-39, 2013. doi:  
400 10.1152/ajpcell.00403.2011.
- 401 21. **García IM, Altamirano L, Mazzei L, Fornés M, Molina MN, Ferder L, Manucha W.** Role of  
402 mitochondria in paricalcitol-mediated cytoprotection during obstructive nephropathy. *Am J Physiol*  
403 *Renal Physiol* 302(12): F1595-605, 2012. doi: 10.1152/ajprenal.00617.2011.
- 404 22. **Giustina A, Adler RA, Binkley N, Bollerslev J, Bouillon R, Dawson-Hughes B, Ebeling PR,**  
405 **Feldman D, Formenti AM, Lazaretti-Castro M, Marcocci C, Rizzoli R, Sempos CT, Bilezikian**  
406 **JP.** Consensus statement from 2nd International Conference on Controversies in Vitamin D. *Rev*  
407 *Endocr Metab Disord* 21: 89–116, 2020.
- 408 23. **Grant WB, Baggerly CA, Lahore H.** Reply: “Vitamin D Supplementation in Influenza and  
409 COVID-19 Infections. Comment on: Evidence That Vitamin D Supplementation Could Reduce Risk  
410 of Influenza and COVID-19 Infections and Deaths *Nutrients* 2020, 12(4), 988”. *Nutrients* 12: 1620,  
411 2020. doi:10.3390/nu12061620.
- 412 24. **Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP.**  
413 Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections  
414 and Deaths. *Nutrients* 12(4): pii: E988, 2020. doi: 10.3390/nu12040988.
- 415 25. **Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP.**  
416 Vitamin D Supplementation Could Prevent and Treat Influenza, Coronavirus, and Pneumonia  
417 Infections. *Preprints* 2020030235, 2020. doi: 10.20944/preprints202003.0235.v1.

- 418 26. **Gruber-Bzura BM.** Vitamin D and influenza - Prevention or therapy? *Int J Mol Sci* 19: 2419,  
419 2018.
- 420 27. **Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux M.** Human serum 25-  
421 hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 77: 204–  
422 210, 2003.
- 423 28. **Hosseini-nezhad A, Spira A, Holick MF.** Influence of vitamin D status and vitamin D3  
424 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical  
425 trial. *PLoS One* 8(3): e58725, 2013. doi:10.1371/journal.pone.0058725
- 426 29. **Kearns MD, Alvarez JA, Tangpricha V.** Large, single-dose, oral vitamin D supplementation in  
427 adult populations: a systematic review. *Endocr Pract* 20: 341-351, 2014.
- 428 30. **Kong J, Zhu X, Shi Y, Liu T, Chen Y, Bhan I, Zhao Q, Thadhani R, Li YC.** VDR attenuates  
429 acute lung injury by blocking Ang-2-Tie-2 pathway and renin-angiotensin system. *Mol Endocrinol* 27:  
430 2116-2125, 2013.
- 431 31. **Laird E, Kenny RA.** The Irish Longitudinal Study of Ageing (TILDA). 2020.  
432 doi.org/10.38018/TildaRe.2020-05.
- 433 32. **Laviano E, Sanchez Rubio M, González-Nicolás MT, Palacian MP, López J, Gilaberte Y,**  
434 **Calmarza P, Rezusta A, Serrablo A.** Association between preoperative levels of 25-hydroxyvitamin  
435 D and hospital-acquired infections after hepatobiliary surgery: A prospective study in a third-level  
436 hospital. *PLoS One* 15(3): e0230336, 2020. doi: 10.1371/journal.pone.0230336.
- 437 33. **Leung PS.** The Modulatory Action of Vitamin D on the Renin-Angiotensin System and the  
438 Determination of Hepatic Insulin Resistance. *Molecules* 24: pii: E2479, 2019.  
439 <https://doi.org/10.3390/molecules24132479>.
- 440 34. **Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J.** Vitamin D: a negative endocrine  
441 regulator of the renin-angiotensin system and blood pressure. *J Steroid Biochem Mol Biol* 89-90: 387-  
442 392, 2004.



- 443 35. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z,  
444 Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L. Clinical  
445 and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci*  
446 *China Life Sci* 63: 364-374, 2020.
- 447 36. Máčová L, Bičíková M, Hampl R. Impaired vitamin D sensitivity. *Physiol Res* 67(3): S391-S400,  
448 2018.
- 449 37. Malihi Z, Lawes CMM, Wu Z, Huang Y, Waayer D, Toop L, Khaw KT, Camargo CA,  
450 Scragg R. Monthly high-dose vitamin D supplementation does not increase kidney stone risk or  
451 serum calcium: results from a randomized controlled trial. *Am J Clin Nutr* 109(6): 1578-1587, 2019.
- 452 38. McCullough PJ, Lehrer DS, Amend J. Daily oral dosing of vitamin D3 using 5,000 to 50,000  
453 international units a day in long-term hospitalized patients: Insights from a seven year experience. *J*  
454 *Steroid Biochem Mol Biol* 189: 228-239, 2019.
- 455 39. Meftahi GH, Jangravi Z, Sahraei H, Bahari Z. The possible pathophysiology mechanism of  
456 cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-  
457 aging". *Inflamm Res* 1-15, 2020.
- 458 40. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D  
459 Deficiency and Treatment with COVID-19 Incidence. *medRxiv* 2020.05.08.20095893, 2020. doi:  
460 10.1101/2020.05.08.20095893.
- 461 41. Mohamed AA, Alawna M. Role of increasing the aerobic capacity on improving the function of  
462 immune and respiratory systems in patients with coronavirus (COVID-19): A review. *Diabetes Metab*  
463 *Syndr* 14(4): 489-496, 2020.
- 464 42. Moradi S, Shahdadian F, Mohammadi H, Rouhani MH. A comparison of the effect of  
465 supplementation and sunlight exposure on serum vitamin D and parathyroid hormone: A systematic  
466 review and meta-analysis. *Crit Rev Food Sci Nutr* 60(11): 1881-1889, 2020.
- 467 43. Panagiotou G, Tee SA, Ihsan Y, Athar W, Marchitelli G, Kelly D, Boot CS, Stock N,  
468 Macfarlane J, Martineau AR, Burns G, Quinton R. Low serum 25-hydroxyvitamin D (25[OH]D)

- 469 levels in patients hospitalised with COVID-19 are associated with greater disease severity. *Clin*  
470 *Endocrinol (Oxf)*. 2020;10.1111/cen.14276. doi:10.1111/cen.14276
- 471 44. **Panarese A, Shahini E.** Letter: Covid-19, and Vitamin D. *Aliment Pharmacol Ther* 51(10): 993-  
472 995, 2020.
- 473 45. **Perret C, Colnot S, Romagnolo B, Thomasset M.** Control of nuclear transcription of vitamin D-  
474 dependent genes by vitamin D. *Curr Opin Nephrol Hypertens* 6(4): 314-20, 1997.
- 475 46. **Pfeffer PE, Lu H, Mann EH, Chen YH, Ho TR, Cousins DJ, Corrigan C, Kelly FJ, Mudway**  
476 **IS, Hawrylowicz CM.** Effects of vitamin D on inflammatory and oxidative stress responses of human  
477 bronchial epithelial cells exposed to particulate matter. *PLoS One* 13: e0200040, 2018.  
478 doi.org/10.1371/journal.pone.0200040.
- 479 47. **Pham H, Rahman A, Majidi A, Waterhouse M, Neale RE.** Acute Respiratory Tract Infection  
480 and 25-Hydroxyvitamin D Concentration: A Systematic Review and Meta-Analysis. *Int J Environ Res*  
481 *Public Health* 16: 3020, 2019. doi:10.3390/ijerph16173020.
- 482 48. **Pilz S, März W, Cashman KD, Kiely M, Whiting SJ, Holick MF, Grant WB, Pludowski P,**  
483 **Hilgsmann M, Trummer C, Schwetz V, Lerchbaum E, Pandis M, Tomaschitz A, Grübler MR,**  
484 **Gaksch M, Verheyen N, Hollis BW, Rejnmark L, Karras SN, Hahn A, Bischoff-Ferrari HA,**  
485 **Reichrath J, Jorde R, Elmadfa I, Vieth R, Scragg R, Calvo MS, van Schoor NM, Bouillon R,**  
486 **Lips P, Itkonen ST, Martineau AR, Lamberg-Allardt C, Zittermann A.** Rationale and Plan for  
487 Vitamin D Food Fortification: A Review and Guidance Paper. *Front Endocrinol (Lausanne)* 9: 373,  
488 2018.
- 489 49. **Pincikova T, Paquin-Proulx D, Sandberg JK, Flodström-Tullberg M, Hjelte L.** Vitamin D  
490 treatment modulates immune activation in cystic fibrosis. *Clin Exp Immunol* 189: 359-371, 2017.
- 491 50. **Quesada-Gomez JM, Entrenas Castillo M, Bouillon R.** Vitamin D Receptor Stimulation to  
492 Reduce Acute Respiratory Distress Syndrome (ARDS) in Patients With Coronavirus SARS-CoV-2  
493 Infections. *Steroid Biochem Mol Biol* 105719, 2020. doi: 10.1016/j.jsbmb.2020.105719.

- 494 51. **Quraishi SA, Bittner EA, Blum L, Hutter MM, Camargo CA Jr.** Association between  
495 preoperative 25-hydroxyvitamin D level and hospital-acquired infections following Roux-en-Y gastric  
496 bypass surgery. *JAMA Surg* 149(2): 112-8, 2014.
- 497 52. **Rhodes JM, Subramanian S, Laird E, Kenny RA.** Editorial: Low population mortality from  
498 COVID-19 in countries south of latitude 35 degrees North - supports vitamin D as a factor determining  
499 severity. *Aliment Pharmacol Ther* 2020. doi: 10.1111/apt.15777.
- 500 53. **Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML.** Serum 25-  
501 hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS*  
502 *One* 5. e11088, 2010. doi:10.1371/journal.pone.0011088.
- 503 54. **Sandhu MS, Casale TB.** The role of vitamin D in asthma. *Ann Allergy Asthma Immunol* 105: 191-  
504 199, 2010.
- 505 55. **Santoro D, Caccamo D, Lucisano S, Buemi M, Sebekova K, Teta D, De Nicola L.** Interplay of  
506 vitamin D, erythropoiesis, and the renin-angiotensin system. *Biomed Res Int* 2015: 145828, 2015.  
507 <https://doi.org/10.1155/2015/145828>.
- 508 56. **Shi Y, Liu T, Yao L, Xing Y, Zhao X, Fu J, Xue X.** Chronic vitamin D deficiency induces lung  
509 fibrosis through activation of the renin-angiotensin system. *Sci Rep* 7: 3312, 2017.  
510 <https://doi.org/10.1038/s41598-017-03474-6>.
- 511 57. **Shirvani A, Kalajian TA, Song A, Holick MF.** Disassociation of Vitamin D's Calcemic Activity  
512 and Non-calcemic Genomic Activity and Individual Responsiveness: A Randomized Controlled  
513 Double-Blind Clinical Trial. *Sci Rep* 9: 17685, 2019. doi:10.1038/s41598-019-53864-1.
- 514 58. **Silvagno F, De Vivo E, Attanasio A, Gallo V, Mazzucco G, Pescarmona G.** Mitochondrial  
515 localization of vitamin D receptor in human platelets and differentiated megakaryocytes. *PLoS One* 5:  
516 e8670, 2010. doi: 10.1371/journal.pone.0008670.
- 517 59. **Sun ML, Yang JM, Sun YP, Su GH.** Inhibitors of RAS Might Be a Good Choice for the  
518 Therapy of COVID-19 Pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 43(0): E014, 2020.  
519 doi:10.3760/cma.j.issn.1001-0939.2020.0014.

- 520 60. **Taher YA, van Esch BCAM, Hofman GA, Henricks PAJ, van Oosterhout AJM.**  $1\alpha,25$ -  
521 Dihydroxyvitamin D<sub>3</sub> potentiates the beneficial effects of allergen immunotherapy in a mouse model  
522 of allergic asthma: role for IL-10 and TGFbeta. *J Immunol* 180: 5211e21, 2008.  
523 doi.org/10.4049/jimmunol.180.8.5211.
- 524 61. **Takano Y, Mitsuhashi H, Ueno K.**  $1\alpha,25$ -Dihydroxyvitamin D<sub>3</sub> inhibits neutrophil recruitment in  
525 hamster model of acute lung injury. *Steroids* 76: 1305-1309, 2011.
- 526 62. **Tan WSD, Liao W, Zhou S, Mei D, Wong WF.** Targeting the renin-angiotensin system as novel  
527 therapeutic strategy for pulmonary diseases. *Curr Opin Pharmacol* 40: 9-17, 2018.
- 528 63. **Tan ZX, Chen YH, Xu S, Qin HY, Zhang C, Zhao H, Xu DX.** Calcitriol inhibits bleomycin-  
529 induced early pulmonary inflammatory response and epithelial-mesenchymal transition in mice.  
530 *Toxicol Lett* 240: 161-171, 2016.
- 531 64. **The association of UK Dietitians:** Covid 19, Coronavirus - Advice for general Public. March 16,  
532 2020. <https://www.bda.uk.com/resource/covid-19-corona-virus-advice-for-the-general-public.html>
- 533 65. **Tian WM, Yang YG, Shang YX, Cai XX, Chen WW, Zhang H.** Role of  $1,25$ -dihydroxyvitamin  
534 D<sub>3</sub> in the treatment of asthma. *Eur Rev Med Pharmacol Sci* 18: 1762-1769, 2014.
- 535 66. **Topilski I, Flaishon L, Naveh Y, Harmelin A, Levo Y, Shachar I.** The anti-inflammatory effects  
536 of  $1,25$ -dihydroxyvitamin D<sub>3</sub> on Th2 cells in vivo are due in part to the control of integrin-mediated T  
537 lymphocyte homing. *Eur J Immunol* 34: 1068e76, 2004. doi.org/10.1002/eji.200324532.
- 538 67. **Trochoutsou AI, Kloukina V, Samitas K, Xanthou G.** Vitamin-D in the Immune System:  
539 Genomic and Non-Genomic Actions. *Mini Rev Med Chem* 15(11): 953-63, 2015.
- 540 68. **Turin A, Bax JJ, Doukas D, Joyce C, Lopez JJ, Mathew V, Pontone G, Shah F, Singh S,**  
541 **Wilber DJ, Rabbat MG.** Interactions Among Vitamin D, Atrial Fibrillation, and the Renin-  
542 Angiotensin-Aldosterone System. *Am J Cardiol* 122: 780–784, 2018.
- 543 69. **Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD.** Renin-  
544 Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med* 382(17):1653-  
545 1659, 2020.

- 546 70. **Vuichard Gysin D, Dao D, Gysin CM, Lytvyn L, Loeb M.** Effect of Vitamin D3  
547 Supplementation on Respiratory Tract Infections in Healthy Individuals: A Systematic Review and  
548 Meta-Analysis of Randomized Controlled Trials. *PLoS One* 11: e0162996, 2016.
- 549 71. **Wacker M, Holick MF.** Sunlight and Vitamin D. A global perspective for health  
550 *Dermatoendocrinol* 5(1): 51-108, 2013.
- 551 72. **Wang Y, Yang Z, Gao L, Cao Z, Wang Q.** Effects of a single dose of vitamin D in septic  
552 children: a randomized, double-blinded, controlled trial. *Int Med Res* 48(6): 300060520926890,  
553 2020. doi: 10.1177/0300060520926890.
- 554 73. **Xu J, Yang J, Chen J, Luo Q, Zhang Q, Zhang H.** Vitamin D alleviates lipopolysaccharide-  
555 induced acute lung injury via regulation of the renin-angiotensin system. *Mol Med Rep* 16: 7432–7438,  
556 2017.
- 557 74. **Xystrakis E, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF, Adikibi T, Pridgeon C,**  
558 **Dallman M, Loke TK, Robinson DS, Barrat FJ, O'Garra A, Lavender P, Lee PH, Corrigan C,**  
559 **Hawrylowicz CM.** Reversing the defective induction of IL-10-secreting regulatory T cells in  
560 glucocorticoid-resistant asthma patients. *J Clin Invest* 116: 146e55, 2006.
- 561 75. **Yao L, Shi Y, Zhao X, Hou A, Xing Y, Fu J, Xue X.** Vitamin D attenuates hyperoxia-induced  
562 lung injury through downregulation of Toll-like receptor 4. *Int J Mol Med* 39: 1403-1408, 2017.
- 563 76. **Zemb P, Bergman P, Camargo CA Jr, Cavalier E, Cormier C, Courbebaisse M, Hollis B,**  
564 **Minisola S, Pilz S, Pludowski P, Schmitt F, Zdrenghea M, Souberbielle JC.** Vitamin D deficiency  
565 and COVID-19 pandemic. *J Glob Antimicrob Resist* 22: 133-134, 2020.
- 566 77. **Zhang H, Yang N, Wang T, Dai B, Shang Y.** Vitamin D reduces inflammatory response in  
567 asthmatic mice through HMGB1/TLR4/NF  $\kappa$ B signaling pathway. *Mol Med Rep* 17: 2915-2920,  
568 2018.

569

## 570 **Legend to Figures**

### 571 **Figure 1**

572 **Cellular interactions of angiotensin and vitamin D receptors**

573 RXR: retinoid X receptor; RAS: renin-angiotensin system; VDRE: Vitamin D response element;  
574 1,25(OH)<sub>2</sub>D<sub>3</sub>: 1,25-dihydroxyvitamin D<sub>3</sub> (20).

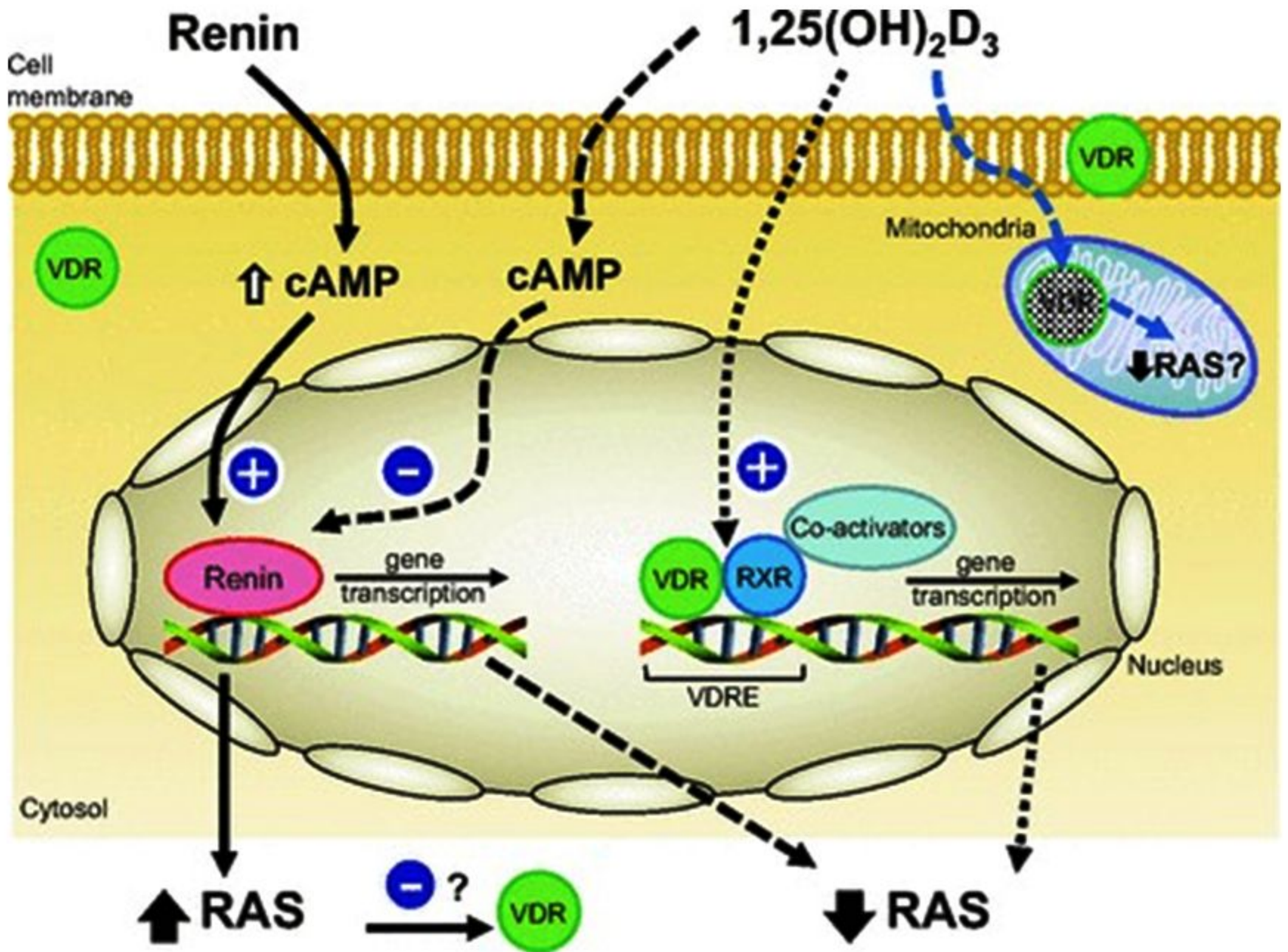
575

576 **Figure 2**

577 **Graphic overview of vitamin D main signaling pathways as a new potential treatment in**  
578 **COVID-19 lung infection**

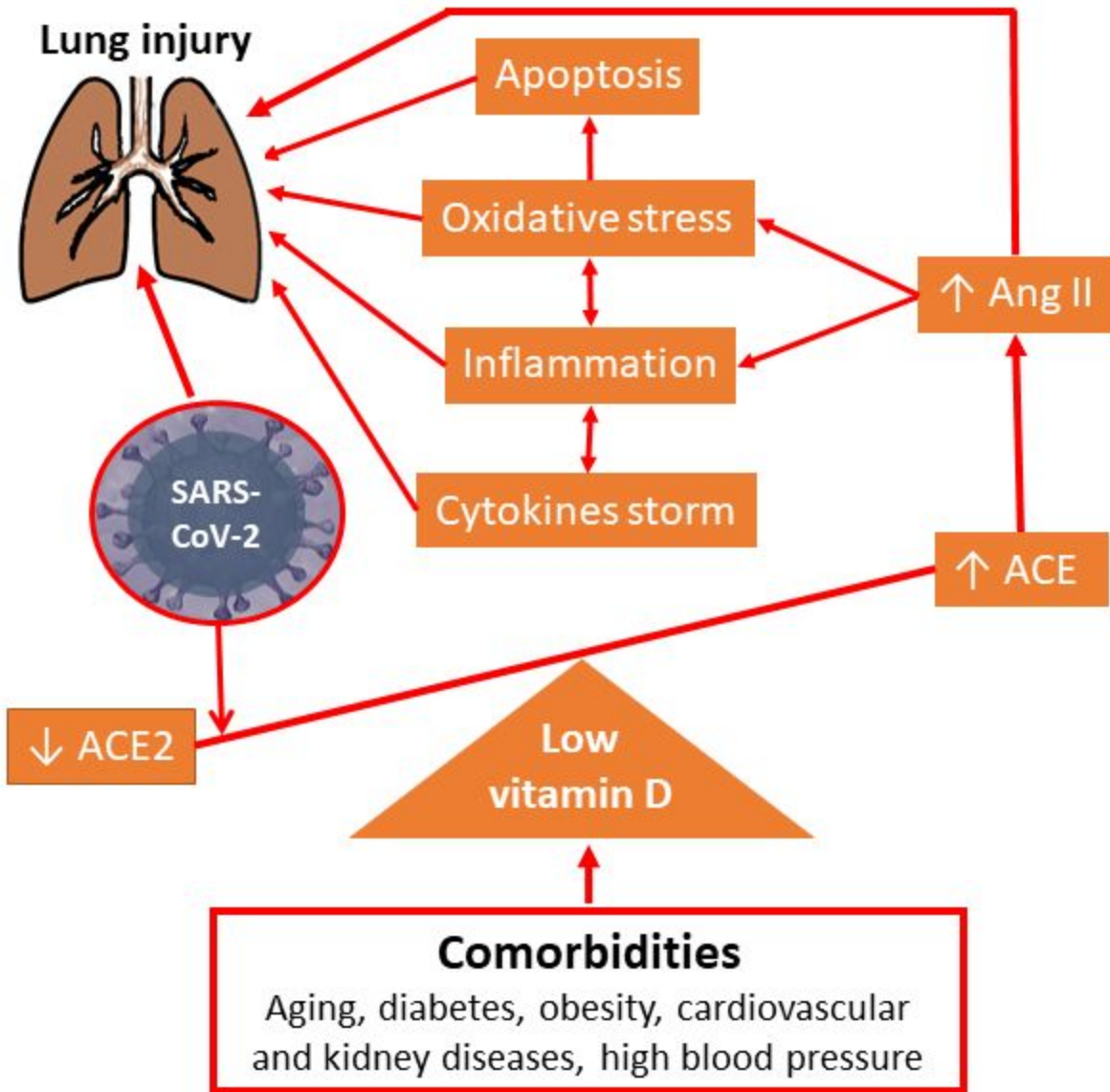
579 Solid lines indicate stimulation/induction, while dashed lines indicate inhibition/blocking.

580





## Low serum level of vitamin D



## High serum level of vitamin D

