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REVIEW ARTICLE

Vitamin D deficiency associates inversely with COVID-19 risks; might avoidance of vitamin D inadequacy reduce those risks?

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ABSTRACT

The risks of COVID-19, whether of becoming infected, needing intensive care or dying, consistently relate inversely to vitamin D status [serum 25(OH)D concentration], but low 25(OH)D is not just due to COVID-19 since they are seen in relation to pre-pandemic 25(OH)D values, both in individual cohorts and across many populations. Furthermore, many recognised risk factors for increased COVID-19 severity themselves reduce vitamin D status [e.g., obesity, dark skin, indoor lifestyles, low socio-economic status and increasing age], which complicates data analyses. Vitamin D has many mechanistic effects likely to provide adjunctive benefits protecting against COVID-19 severity. For example, vitamin D reduces the risks of microbial infection by promoting innate immunity and reduces tissue damage in severe infections by modulating the severity of adaptive immune responses. The protective mechanistic effects of correcting vitamin D inadequacy discussed support the view that increasing vitamin D status should reduce COVID-19 risks. However, many trials of cholecalciferol treatment have failed to do so, probably because it takes many weeks to raise serum 25(OH)D levels adequately whilst the increasing clinical use of the 25(OH)D metabolite [calcifediol] in COVID-19 treatment, which raises serum 25(OH)D concentrations rapidly, has led to reports of clinical benefits in COVID-19 illness.

Introduction

The severity of COVID-19 illness, the need for hospitalisation, for intensive care and COVID-19 mortality are increased in those with vitamin D deficiency at presentation[1,2]. Since severe infections could reduce the serum 25-hydroxyvitamin D [25(OH)D] concentrations that are used to assess repletion[3] this data does not provide evidence of causality of vitamin D deficiency for increasing COVID-19 risks. However, data for vitamin D status [serum 25(OH)D concentrations] pre-pandemic relates inversely to COVID-19 illness severity prospectively. For example, in a middle-eastern study of 253 hospitalised COVID-19 patients with pre-pandemic 25(OH)D data, a 25(OH)D <20 ng/mL [deficiency] was commoner in severe illness [87.4%]) than in milder illness [34.3%; $p < 0.001$) and those with deficiency were more likely to have severe/critical illness than those with 25(OH)Ds ≥40 ng/mL (OR=14:[95% confidence interval [CI];4-51; $p< 0.001$)[4].

In a retrospective study of >190,000 adults from the 50 states in the USA, serum 25(OH)D values measured during the twelve months before COVID infections began were examined in relation to later COVID-19 risks [assessed by SARS-CoV-2 testing] between mid-March and mid-June 2020. Strong inverse correlations were found between pre-pandemic serum 25(OH)D and later SARS-CoV-2 infection rates [R^2;0.96] across all areas of residence in the USA, all latitudes, ages and ethnicities and in both genders: a correlation that persisted after adjustment for the other COVID-19 risk factors identified. SARS-CoV-2 infection rates ranged from 12.5% with pre-pandemic 25(OH)D values of <20ng/ml] to 5.9% with pre-pandemic 25(OH)D values of >55ng/ml. Thus, SARS-CoV-2 infection rates were halved in adults with the highest vs. the lowest vitamin D [VitD] status across the USA[5]. Global infection rates have been examined against known pre-pandemic VitD deficiency rates in 19 European countries; the highest Covid risks were found in countries with the highest pre-pandemic vitamin D deficiency rates and the higher the mean population 25(OH)D the lower the mortality rate [after adjusting for age and year of the pandemic] up to mean 25(OH)D concentrations of 50 nmol/l. The risks across northern Scandinavia were 'unexpectedly' low, but so were their VitD deficiency rates – each of those countries having ongoing public health initiatives for improving their populations vitamin D status[6]. Warm Mediterranean countries [e.g Spain & Italy] and tropical countries also had high SARS-CoV-2 rates together with high deficiency rates[7,8].

In addition, better VitD status at baseline was significantly associated with reduced COVID-19 rates, prospectively, in a randomised controlled trial [RCT] of supplementation at 4000 IU D3 for 30 days which significantly reduced COVID-19 infection risks in heavily SARS-CoV-2 -exposed front-line health workers assessed on day 45, [RR=0.23[95%CI: (0.09-0.55)[9].

Together, these findings suggest that VitD provision for reducing subsequent COVID-19 risks warrants formal consideration. This commentary, therefore, aims to provide further justification for avoiding VitD deficiency from mechanistic and other evidence.

Innate defence responses and vitamin D deficiency. Innate immune responses provide vital protection against

microbial infections, bacterial, viral or fungal, through rapid increases in the production of compounds that lethally disrupt those pathogens, including the defensins, from both neutrophil and lymphoid cells, and these responses are promoted by vitamin D. Cathelicidin[LL-37], also secreted by immune cells and by epithelial cells lining both lungs and gut, acts similarly but has broader immunomodulatory effects and blocks viral replication in several ways[10]. Higher circulating cathelicidin levels are promoted by vitamin D and associated with lower circulating inflammatory factor IL-17 levels. Since IL-17 has adverse effects on both vascular and lung epithelia, cathelicidin reduces the risks of COVID-19-induced intra-vascular thrombosis and acute respiratory distress syndrome [ARDS][11].

SARS-CoV-2 organisms are thought to evade some early innate immune responses, helping to explain their high infectivity[12], a phenomenon likely explained by their early binding to membrane-bound [mACE2] endothelial ACE2 molecules, which allows SARS-CoV-2-spike protein to damage lung endothelium by downregulating ACE2 synthesis. However, ACE2 secretion is increased by vitamin D and reduces infective lung damage experimentally[13], as it will in human COVID-19 illness.

Vitamin D and renin angiotensin system overactivity. Calcitriol down-regulates renin-angiotensin-aldosterone system activity [RAAS] by renin gene suppression[14], which reduces lung RAAS overactivity induced by infection[15]. It also upregulates the ACE2 gene and ACE2 suppresses many adverse effects of RAAS system overactivity in the lungs, protecting both their vasculature and endothelium. These effects are associated, experimentally, with reduced risks of developing ARDS, and since they are relevant to human COVID-19 illness severity[16], this makes VitD repletion desirable for protection against COVID-19 illness severity.

Furthermore, vitamin D_3 [$VitD_3$] increases secretion of the defensins, and, since defensins destroy the structure of pathogenic organisms, deficiency will increase the risks of chest infections. Defensins also contribute to regulation of pro/anti-inflammatory cytokine secretion. Unsurprisingly, therefore, those most VitD replete are the most likely to escape COVID-19 illness or, if infected, to be less severely affected, as suggested by data mentioned in the Introduction[1,2 4-6].

Following tissue invasion by pathogens, innate immune defence mechanisms are triggered through intracellular immune cell pattern recognition receptors [PRRs][17], that detect 'pathogen-associated molecular patterns' [PAMPs]. The further immune responses that follow help prevent excessive tissue damage, by suppressing pro-inflammatory cytokine production [e.g., TNF-alpha & IL-6] and by upregulating anti-inflammatory cytokine secretion [e.g. IL-10][18,19].

The induction of antigen-presenting dendritic cells from monocytes, whose PRRs recognise pathogen fragments, leads to the development of adaptive[acquired] immunity with specific antibody formation against pathogens being destroyed, by cells that can then re-secrete those antibodies in any future reinfection with specific organisms because

they retain their recognition of specific PAMPS[20]. This mechanism is taken advantage of in mass immunisation schemes to avoid future infections by immunisation, using suitable microbial component vaccines to induce acquired immunity. This is routine for childhood illnesses [e.g., measles, mumps and rubella], providing life-long protection. For COVID-19 illness immune protection lasts only months to ~2 years after vaccination or infection and infections with newer SARS_Co-V-2 variants are not necessarily prevented[21]. The improvement of natural immune defences is, therefore, a highly desirable target to aim for in protecting communities against COVID-19, or any future pathogenic infecting microbe that could trigger future pandemics; The potential for adequate VitD status to reduce risks of COVID-19, or any similar future infection is, therefore, worthy of consideration at the population level.

Vitamin D formation and activation.

Cholecalciferol [$VitD_3$] forms in skin by condensation of 7-dehydro-cholesterol [as does vitamin D_2 from ergosterol in plants/fungi - not discussed further] when irradiated by $UVB_{280\text{-}320\ nm}$ in sunlight, transported into the circulation and taken up by the liver, where most 25-hydroxyation takes place, forming 25(OH)D. This metabolite then circulates where, with its ½ life of several weeks, its concentration provides a guide to the adequacy of body stores and is used for clinical assessment of VitD status. The 25(OH)D metabolite is also the substrate for a second hydroxylation to form activated vitamin D [1α,25-dihydroxyvitamin D; calcitriol] [3l. This activation, first detected in the kidneys[22], provides the circulating [hormonal] calcitriol necessary for maintenance of bone health [not further discussed]. However, the same activating enzyme, [CYP57B1] is present, and active, in the many other tissues that express vitamin D receptors [VDR], including the immune system[23], and intracellular calcitriol has autocrine and paracrine effects in immune system cells that induce the well-known actions of VitD on innate and adaptive immunity[24].

Risk factors for COVID-19. COVID-19 severity is consistently reported as being more likely and more serious in people with pre-existing illnesses [e.g, respiratory, circulatory and renal disorders]. High risk factors also include obesity, older age, diabetes, being immune-compromised, health service work, living in residential care, working shifts and having dark skin[25]. It is noteworthy that most of those groups are also accepted to be at increased risk for VitD deficiency. In obesity this is because hepatic 25(OH)D synthesis is reduced and fat stores of VitD are enlarged[26]; in older age because dietary intake, skin synthesis and gut absorption are variously reduced[27]; in residential care, shift work and health care work, indoor lifestyles and using covered up clothing, where exposure to sunlight is limited, while melanin in dark skin is a powerful sunscreen, each increasing vitamin D requirements[28]. Also, UVB availability in temperate climates is low, with none in winter which worsens VitD deficiency risks[29].

Mechanistic effects of vitamin D relevant to COVID-19. VitD suppresses the renin gene, thereby reducing renin-angiotensin-aldosterone [system [RAAS]

overactivity, [seen in severe COVID-19 illness] and upregulating ACE2/Ang[1-7] activity which has both anti-inflammatory and antioxidant effects in the lung, thereby reducing the risks of acute respiratory distress syndrome [ARDS] with its high mortality rates. Together these data mean that VitD repletion should reduce the risks of severe lung damage in COVID-19 illness. Further non-canonical pathways for VitD activation and novel metabolite formation are being reported but not yet fully characterized, but may prove of importance for COVID-19 illness[30].

Lung damage in infections, including SARSCoV-2, increases with concomitant kidney disease since renal damage reduces KLOTHO production. Klotho normally acts to maintain adequate endogenous antioxidant activity in the lungs through cellular Nrf2 pathway activation which reduces excessive oxidative stress and inflammation through various actions including increasing superoxide dismutase [SOD1] secretion. SOD1 contributes to antioxidant response regulation and has vital roles in cell survival, including prevention of anoxic lung damage[31]. Therapeutic agents for boosting aKLOTHO production are, therefore, being intensively sought for protecting many tissues[32]. However, VitD is already known to increase both Klotho secretion, and Nrf2 pathway activity, both of which have protective effects on the lungs[33], a benefit of VitD repletion which should provide a useful adjunctive measure in COVID-19 management.

Vitamin D's known effects on the immune system include promoting T cell shifts promoting the formation of regulatory T calls. Both cytotoxic T lymphocytes and B cells, when activated, increase their vitamin D receptor [VDR] production making upregulation of VDR signalling pathways by activated $VitD_3$ [calcitriol], part of the innate immune response[33,34].

Genomic and non-genomic actions of activated vitamin D. Activated vitamin D [calcitriol] has both genomic and non-genomic effects. Genomic effects follow calcitriol binding to VDR:RXR receptor complexes that enter cell nuclei and bind to VitD response elements [VDREs] in the gene promoter regions of ~ 20,000 genes, and many act to regulate gene expression. Gene upregulation is common, increasing mRNA production and VDR-binding transcription factor formation. Gene downregulation is less common but more complex and induced by many mechanisms that mostly inhibit transcription factor formation[35]. Non-genomic calcitriol effects follow its binding to cell wall caveolar VDRs, inducing rapid increases in intracellular concentrations of ionised calcium and rapid changes in intracellular metabolism [e.g, protecting islet beta cells from tissue damage, suppressing hepatic lipid synthesis, and reducing the release of lipids and glucose from the liver under metabolic syndrome conditions experimentally][36,37,24].

Vitamin D and severity of COVID-19 illness. Overall, inadequate VitD provision allows inflammatory lung responses to infection to become excessive, increasing the risks of the development of cytokine storms with their uncontrolled overproduction of pro-inflammatory cytokines[38]. The increasingly severe inflammatory lung damage that follows can rapidly progress to ARDS

which is often fatal and, experimentally, VitD deficiency increases infection severity with rapid increases in inflammation, as seen in severe COVID-19 illness[39]. Experimentally also, adequate VitD protects against ARDS severity by reducing TNF alpha, interleukin-6, interferon-gamma and myeloperoxidase secretion in the lungs and by downregulating pro-inflammatory pathway activity. These changes are relevant to the increased risk of ARDS in severe human COVID-19 infection and, it should be noted, there is a known requirement for activated VitD [calcitriol] for suppression of cytokine-induced inflammation that is 'critical'[11].

Though VitD deficiency co-exists with COVID-19 at presentation, viral illness could well induce reductions in 25(OH)D concentration so that this association could reflect reverse causation rather than being causal. However, it has consistently been noted that risk factors for VitD deficiency and for COVID-19 are similar[40]. Also, as mentioned in the Introduction, the higher the deficiency rates pre-pandemic in population-based studies the greater the subsequent COVID-19 illness rates, the need for hospital care and the higher the mortality in COVID-19[6]. Of all the other risk factors mentioned that are associated with increased COVID-19 risks, [e.g., obesity, increased age, low socio-economic status, air pollution and diabetes as well as pre-existing illness][41-43]. VitD deficiency would be the easiest [and cheapest] to correct. This makes it important to determine whether the potential for adequate VitD status to reduce COVID-19 risks through its multitude of well understood effects on cell function translates into significant clinical benefits. The data on inverse relationships between VitD status and COVID-19 severity, observationally, is consistent and, if it were to be accepted as justifying a drive to avoid VitD deficiency, this might provide a more useful test of causality than efforts directed at carrying out randomised controlled trials since community data is likely to be compromised by many difficulties and by ongoing vaccination programmes[44], while achieving adequately designed trials of VitD supplementation in hospitalized COVID-19 illness patients is hampered by both pressure of work and by the severity of COVID-19 illness; for example, around 20% of hospitalised COVID-19 patients can be on mechanical ventilation[45].

Correction of vitamin D inadequacy.

In considering trying to improve VitD status in the future, some countries have already achieved higher VitD status than others, with reductions in their overall COVID-19 risks[6]. For other countries to follow suit it would help to have general agreement on minimal serum 25(OH)D concentration targets, to know what vitamin D3 intakes are needed to get adults to that target value, and how best to achieve such intakes, in each different population group.

Foods are a poor source of vitamin D, egg yolks contain 40-60 IU, depending on hen feeds; meat contains some of the 25(OH)D metabolite [calcifediol]; fish contains variable amounts of $VitD_3$, though many fishes do not synthesize it, but depend instead on vitamin D_3 provided by the primeval unicellular organisms at the bottom of the food chain that first evolved its synthesis, though some oily fish are good sources, [e.g herrings, mackerel, sardines, wild salmon and pilchards]. Dairy foods contain too little $VitD_3$ for bone health.

In world-war 2 [WW2] UK fatty spreads were fortified to match butter content and many fatty spreads still contain some added $VitD_3$. Pregnant and nursing mothers and children under 5 were supplied with 5 extra 'welfare foods' in the UK during WW2 which abolished rickets [extra milk, meat, eggs, orange juice and cod liver oil] a provision ending in 1959[46]. Milk, fatty spreads and orange juices may be fortified, as in the USA, but diet cannot ensure repletion unless there is a food fortification programme in place. In Finland, for example, voluntary fortification of dairy foods was introduced ~20 years ago. When audit showed provision to be inadequate after ~10 years, the amounts added were doubled. Since then, audit has shown that most of the population achieves repletion apart from recent immigrants, elders and those in residential care, all of whom are now given additional supplements[47,48]. Flour fortification has been suggested as a cost-effective measure for preventing VitD deficiency in the UK but not introduced[49].

Reasons for high population VitD deficiency rates [excluding specific illnesses and medications that lower serum 25(OH)D] are mentioned above. Further obvious factors aggravating deficiency, across entire populations, include the increasing use of sunscreens for fear of skin cancer and to reduce skin ageing, and the addition of sunscreen to most facial cosmetics. In tropical countries sun may be avoided for comfort and because paler skin can be regarded as desirable. Children may be kept indoors to keep cool, aggravating the risk of rickets and outdoor and agricultural workers are the least likely to be VitD deficient in many poorer countries. The increasing use of covered up styles of clothing, especially by women, for modesty, religious or social reasons, also increases deficiency rates in both hot and temperate climates, especially as many followers of these practices are dark-skinned.

Supplementation requires effort by individuals who need to remember to acquire and to take them, even with free provision. From the public health point of view it is comparatively simple to inform communities of their need to take supplements but this has to be repeated at intervals to remain effective[50]. Taking cholecalciferol is effective but slow, taking weeks to months to raise serum 25(OH)D values adequately[51]. Communities have been informed through the media, intermittently, about the benefits of VitD supplements for supporting immune defences during the COVID-19 pandemic. Such publicity clearly increased UK supplement use since it was followed by obvious, though transient, emptying of shelves of VitD containing products in pharmacies and supermarkets when first produced[52,53].

One would expect sunshine, which is the most efficient way to acquire VitD, to be best way to increase VitD provision since, when the sun is high in the sky and UVB reaching the land is maximal, $VitD_3$ synthesis in pale skin can be high. Holick's rule, adjusted for Boston summer sunshine, states that each exposure to ¼ the minimal erythemal dose over ¼ of the body induces VitD3 formation equal to taking 1320 IU of oral $VitD_3$[54]. Human evolution caused those leaving the tropical African areas where humankind first appeared for cooler Northern areas to develop pale skin, an adaptation which has not had time to develop in migrants making similar moves more recently[55]. Modern indoor lifestyles,

including sun avoidance, are further reducing opportunities for skin synthesis of $VitD_3$. Supporting these comments, tribal peoples living early lifestyles in tropical countries regularly have much higher levels of circulating 25(OH)D [100-150nmol/l] than any other population[34].

Variations in guidance on desirable vitamin D status. Recommendations for minimal VitD status [serum 25(OH)D concentrations] for health vary widely as do recommended intakes. The UK advises 25(OH)D levels of 50 nmol/l be achieved with $VitD_3$ intakes of 400-600 U/day though it is almost impossible to get enough VitD from foods to meet those recommendations.[56] For adequate immune function serum 25(OH)D values ≥50 nmol/l are advised by the European Food Safety Authority and by the American Institute of Medicine, with $VitD_3$intakes ≥800 IU/day to maintain such levels, while ≥75 nmol/l is advised by the American Endocrine Soc. Threshold 25(OH)D values necessary for many non-bony health benefits vary[57] and can be >75 nmol/l, [e.g., >100 nmol/l, needing intakes of 4000 IU/day over time, reduces Type 2 diabetes risks in VitD deficiency in people with pre-diabetes][58,59]. Larger VitD intakes than the 400-800 IU/day intakes often advised are recommended for correcting deficiency [e.g., in the UK][51], and since deficiency remains common globally, revised public health guidance is needed on vitamin D intakes[60].

Also, since current guidance on VitD intakes has clearly failed to achieve repletion, in most countries, such guidance needs to be accompanied by public health programmes designed to ensure that the advised intakes are achieved, probably requiring combinations of food fortification and targeted supplementation, as in Finland. Such programmes would have to be acceptable to, and effective in, each countries' population. This is important not only for musculo-skeletal health but for COVID-19 protection since this new infection is persisting world-wide. Furthermore, the continuing emergence of new variants means that current immunisation programmes may not remain protective should more virulent strains develop. Optimising immune defences at the population level is, therefore, highly desirable.

Problems with using cholecalciferol for treating COVID-19. Treatment with cholecalciferol has not generally been effective against COVID-19 illness nor has it improved COVID-19-illness outcomes in most trials[50]. The problem with $VitD_3$ treatment is that its administration, by any route, takes weeks to months to raise serum 25(OH)D values to adequate levels. Thus, benefits for Covid-19 illness in deficiency are unlikely to develop in time to affect hospitalised Covid-19 patient outcomes since they depend on intracellular calcitriol formation, which, being correlated with serum 25(OH)D concentrations, also take weeks or months to be maximised. Increasingly large doses of D3 have been used in COVID-19 illness and have mostly failed to improve outcomes including bolus doses of 1 million IU of $VitD_3$[63]. However doses this high have been unable to prevent rickets due to the reductions in hepatic 25-hydoxylation of D3 they induce[64], probably evolved as protection against $VitD_3$ toxicity with tropical sunshine exposure.

Calcifediol [25(OH)D] treatment for COVID-19. Interestingly, in a relatively small trial in Indian COVID-19 patients with moderate to severe lung problems, many co-morbidities and with VitD deficiency, [serum 25(OH)Ds <50 nmol/l] , those given single oral bolus doses of 500,000 IU of $VitD_3$, increasing their serum 25(OH)D to >50nmol/l, showed significantly reduced mortality one month after dosing, at 24% vs 44% in controls][65]. Similar results were reported after single oral bolus doses of 400,000 IU of $VitD_3$, with significantly reduced COVID-19 mortality at 2 weeks [HR=0.39(95% CI 0.16-0.99)]. Thus, it may be that smallish $VitD_3$ bolus dosing can be effective while doses of 1,000,000 IU or more lose efficacy.

In contrast to the above difficulties, treatment with the 25(OH)D metabolite, calcifediol, now available as an oral slow-release preparation, should prove more effective for COVID-19 than $VitD_3$ because large doses do not induce defects in its processing and serum levels rise rapidly with oral dosing, ensuring that provision of the 25(OH)D substrate to the tissues for activation increases rapidly. This means that intracellular calcitriol also increases rapidly since that process tracks serum 25(OH)D concentrations[24,67]. This expectation, predictable from what is known about the processing of VitD and its effects, is already being met since its use in COVID-19 illness is currently suggesting clinical benefit. For example, in 288 COVID-19 patients where severity of illness and length of hospital stay were inversely related to VitD status on admission, rapid achievement of adequate VitD status with oral calcifediol was followed by significantly shortened hospital stays and by reduced death rates at 22% compared to 40% in untreated controls[67].

Overall, reviewing the available literature, it is apparent that patients with the highest baseline 25(OH)D values at diagnosis and those given calcifediol have had the best COVID-19 related outcomes to date[67], and this comment is supported by further reports. One reviewed the effects of macro-nutrient and micro-nutrient intakes on COVID-19 and found that a majority of previous studies had identified vitamin D as one of several micro-nutrient, which, together with increased plant consumption had beneficial effects on COVID-illness risks[68], a finding that is in line with the earlier reports mentioned in the Introduction. Furthermore, data from the large UK-Biobank cohort has suggested reduction in COVID-19 risks in subjects reporting regular use of vitD containing supplements at recruitment, many years pre-pandemic[69].

It seems likely that the clinical use of oral calcifediol for COVID-19 will increase rapidly as it corrects deficiency faster than D_3 and there is a linear relationship between dosage and achieved serum 25(OH)D. Calcifediol also increases the provision of the 25(OH)D substrate directly to the tissues for activation rapidly, and blood levels are independent of liver 25-hydroxylation. Furthermore, calcifediol is more hydrophilic than $VitD_3$, making calcifediol effective in raising serum 25(OH)D in obesity without the need to increase dosages 2-4-fold as would be required using VitD3 in those who are overweight or obese[70].

Recommended calcifediol dosages are up to 10 microgram/day for both adults and children over 11 years old. For urgent

treatment, and for correcting deficiency quickly, oral doses should be adjusted according to serum 25(OH)D measurements so that the desired serum 25(OH)D concentrations are achieved quickly[71,72]. A recent meta-analysis of 16 studies reports significant risk reductions in overt COVID-19 illness with calcifediol supplementation, prospectively, and also a reduction of ~50% in the proportion of patients needing intensive care which supports the view that avoidance of VitD deficiency is protective against COVID-19 severity[72,73].

In conclusion.

Evidence is building that supports the suggestion, made throughout the COVID-19 pandemic, that avoidance of vitamin D inadequacy is a way to reduce COVID-19 risks by up to 50%. This evidence comes from the known mechanisms of action of activated VitD [calcitriol] on the immune system and from large-scale prospective studies of pre-pandemic VitD status against later covid risks. It also comes from studies of treating COVID-19 patients with oral calcifediol [25(OH)D], which increases serum 25(OH)D concentrations rapidly [hours] while giving $VitD_3$ takes weeks to months. Since intracellular calcitriol [activated VitD] formation tracks serum 25(OH)D concentrations, oral calcifediol can induce rapid changes in immune processes modulated by calcitriol and known to improve immune defences. Ideally, therefore, calcifediol should be used in any future trials of vitamin D in the management of COVID-19 illness. It should also be considered, routinely, for use as an adjunctive measure in the clinical management of COVID-19 pending the development of specific treatments and of vaccines providing life-long protection.

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