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Commentary:- Vitamin D for reduction in Covid-19 risks for south Asian and other vitamin D deficient groups?

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ABSTRACT

Over 7 million people died of COVID-19 globally in the current pandemic. Westernised countries reported increased COVID-19 illness with increased mortality rates in their South Asian and Black communities, while dark-skinned communities are more severely vitamin D deficient than others in westernised countries. Vitamin D has many proven mechanistic effects protective against infections and against the 'acute respiratory distress syndrome' that caused many COVID-19 deaths. This 'commentary', therefore, considers prospective evidence for reductions in COVID-19 risks with better vitamin D repletion; whether treating deficiency reduces COVID-19 risks, and discusses the many actions of vitamin D that could lead to such risk reductions.

Better pre-pandemic vitamin D status predicted ~50% COVID-19 risk reductions in each US state [in ~400,000 adults] and in health care staff. Governments generally resisted calls for higher vitamin D intakes [at 1000-2000 IU/day], quoting 'lack of randomised controlled trials', and fear of vitamin D 'toxicity', despite safe unsupervised population intake generally advised being 'up to 4000 IU/day'. The UK has since recommended daily adult intakes of 400 IU/day, helpful, but too small to correct deficiency. American rules on 'medical need' meant banning treatment of COVID-19 with vitamin D so that the new mRNA vaccines could be used. More recently, trials treating COVID-19 illness with vitamin D_3 [at 1,000,000 IU over 2 weeks] or with the vitamin D 25(OH)D metabolite, calcifediol [at ~2.0mg over 1 month] have shown significantly reduced Covid-19 severity and mortality. This information makes a cogent case for ensuring vitamin D sufficiency globally, most especially in dark skinned communities, as a cost-effective measure for reducing the risks from future COVID-19 variants and from the future health risks of newly emergent pathogenic viruses.

Introduction

The World Health Organisation reported over 775 million cases of COVID-19 illness with >7 million deaths in the recent pandemic by mid-July 2024.[1] The UK and other Westernised countries first reported higher COVID-19 illness and mortality rates in their South Asian and Black communities early in 2020.[2] Factors thought to account for those increases included socio-economic deprivation, overcrowded living conditions, working in crowded sites and care homes, shops and other essential services where self-isolating was virtually impossible.[3] Chronic illnesses were also associated with increased COVID-19 morbidity and mortality across 51 countries.[4] Obesity and type 2 diabetes [T2DM] are more common amongst Black and south Asian peoples than in indigenous White communities in Westernised countries and are associated with increased risks of severe COVID-19 illness and with hospital admission for ventilatory support.[2,5-7]

British national health service [NHS] hospital staff of Black and south Asian origin had higher COVID-19 mortality rates than White staff working in identical conditions,[8] possibly reflecting their increased T2DM, obesity and chronic illness rates. Chronic ill-health was also associated with increased COVID-19 risks in UK Biobank data on ~400,000 representative adults.[9]

Socio-economic deprivation was not an independent predictor of COVID-19 in UK Biobank data analysis.[10] However, a baseline record of regular consumption of vitamin D supplements in the UK-Biobank study was associated, prospectively, with significantly reduced COVID-19 risks.[11]

The vitamin D deficiency pandemic is another health problem, globally, and most severe in Black and south Asian groups.[12-14] Deficiency rates are also high in economically disadvantaged countries.[15]

The aim of the present commentary is, therefore, to report on current evidence for the associations between vitamin D provision and the risks of COVID-19, on the mechanisms that could account for such associations, and on the use of vitamin D for treating COVID-19 illness.

Methods

Data bases [mainly PubMed] were searched for relevant reports using the terms 'vitamin D' and 'COVID-19', together with combinations of the terms 'deficiency, supplementation, health care staff, Black, south Asian, trials, randomised controlled trials, mortality, UK-Biobank, immune responses, mechanisms, acute respiratory distress syndrome, 'cytokine storm'.

Results

Many Asian countries show vitamin D deficiency rates that relate directly to COVID-19 infection rates and to COVID-19 mortality rates. Those rates also relate inversely to vitamin D status [serum 25(OH)D concentration], even after adjustment for confounders, across many Asian countries.[16] Data from 47 countries reported vitamin D deficiency rates of 6.9-81.8% and 2.0-87.5% in 21 European and 24 Asian countries respectively. The direct correlations between deficiency rates and those of COVID-19 illness and of COVID-19 mortality were significant in the Asian but not in the European countries.[17]

African American deficiency rates are 15-20 times higher than those of other Americans.[18] Genetic variation within vitamin D pathways may account for some of the differences seen in vitamin D status between south Asian, Black, and other subjects,[19] but such staff have consistently been the most deficient amongst NHS workers, as in one large NHS Hospital Trust; that trust later found a U-shaped association of serum 25(OH)D with COVID-19 sero-positivity, while confirming the findings for south Asian and Black workers.[20] That unconfirmed U-shaped association might reflect increased COVID-19 risks, [or better antibody responses to COVID-19 exposure] with higher vitamin D status.

South Asian and Black Britons have needed COVID-19-related critical care more often than others. By

July 2020, 260 UK hospitals data showed that Black and south-Asian people had had 36% and 26% higher age-adjusted admission rates, respectively, for COVID-19-related critical care than other groups and had accounted for 25% of all the COVID-19 admissions though being only 11% of the population.[21]

UK Biobank data for >500,000 representative UK adults revealed significant associations between baseline vitamin D deficiency and COVID-19 diagnoses that were abolished by adjustment for ethnicity, obesity and T2DM.[22] But, since each of those 3 factors specifically increase deficiency rates, [reduced 25-hydroxylation of vitamin D in hepatic and other tissues being a feature of both obesity and T2DM], those adjustments have been challenged.[23-25]

Vitamin D prescribing habits [between mid-January and mid-February 2021] reported by questionnaire from 44,440 active clinicians, mostly in Asia, showed that vitamin D had been prescribed by >80% of general practitioner's pre-pandemic and that 72.8% of them planned to prescribe it for COVID-19 illness.[26]

VITAMIN D AND VACCINATION.

Adequate vitamin D status improves antibody responses to immunisation in the elderly.[27] While antibody responses to SARS-CoV-2 vaccines were affected by many factors in the COVIDENCE trial, the risks of remaining sero-negative post-COVID-19-vaccination were significantly reduced by vitamin D supplementation [aOR 0.7; 95% CIs, 0.50-0.9].[28]

MECHANISTIC EFFECTS OF VITAMIN D RELEVANT TO COVID-19 RISK.

Vitamin D has well-understood protective effects against bacterial and viral infection and against the 'acute respiratory distress syndrome' [ARDS] that caused many COVID-19 deaths. These effects include increasing the secretion of the microbiocidal defensins and cathelicidin (LL-37).[29] Vitamin D also reduces pro-inflammatory cytokine production, increases anti-inflammatory cytokine production and prevents excessive innate immune reactions, thereby reducing the risks of cytokine storms.[30,31]

Sars-C0-V-2 organisms may evade early innate immune responses through spike-protein binding to membrane-bound ACE-2 molecules, which reduces lung ACE-2 secretion, causing endothelial lung damage. Vitamin D stimulates ACE-2 secretion which reduces this lung damage, as has been confirmed experimentally.[32,33]

Over-activation of the renin-angiotensin system [RAS] by COVID-19 infections damages the lungs and their vasculature but vitamin D reduces this damage by inhibiting renin secretion.[34,35] The Vitamin D-induced increases in ACE2 secretion also suppress many adverse effects of RAS overactivity, which helps to reduce ARDS risks, as already mentioned. Different genetic profiles of the RAS in Black people could contribute to their increased susceptibility to COVID-19.[36] A further recently identified protective mechanism is that calcifediol suppresses the secretion of a papain-like protease enzyme (PLpro) by COVID-19 organisms, since that enzyme is critical for inducing lung damage.[37]

EPIDEMIOLOGIC EVIDENCE FROM PRE-PANDEMIC DATA.

Baseline serum 25(OH)D concentrations up to ~50 nmol/l in the pre-pandemic year marked significant and progressive reductions in later COVID-19 illness rates, across all regions and all states in the USA, using data on ~400,000 adults.[38] These data together with other similar studies have suggested that repletion of whole populations could greatly reduce COVID-19 illness rates[39]

Discussion

Despite all the evidence, concerted calls by vitamin D workers for modest improvement of vitamin D provision in the UK [to 1000-2000 IU/day] were resisted, governmental bodies citing the lack of relevant RCTs and quoting the potential for vitamin D toxicity, even though maximum unsupervised intakes advised for the general population in the UK [and by the American National Institutes of Health], are 4000 IU/d.[40,41] Current vitamin D intakes advised for UK adults were raised to 400 IU/day all year round.[42] That intake, however, is much less than is

advised for treating deficiency in UK adults.[43] Since deficiency is more severe in dark-skinned than white-skinned Britons, 400 IU/day should not be expected to reduce their increased COVID-19 risks. Similar situations must exist in many other countries since vitamin D deficiency remains common at all latitudes, globally; that deficiency being due to increasingly indoor lifestyles, the widespread use of covered up clothing, lack of sunlight, sun avoidance and the paucity of vitamin D in the diet.[44]

In the USA a further factor inhibiting provision of any measure for improving vitamin D status was that new mRNA vaccine usage was only authorised because of 'unmet medicinal need'. This meant that recognition of any 'treatment' as reducing COVID-19 risks would have prevented their being approved for use in the pandemic.[45]

POTENTIAL BENEFITS OF VITAMIN D REPLETION IN THE FUTURE.

COVID-19 illness has recently become less severe, probably due to reduced virulence of newer variants and regular vaccination of those at high COVID-19 risk, though no vaccine has long-lasting benefits.[46] Interestingly, the public in the UK responded to media reportage on the vitamin D situation by clearing the shelves of supermarkets and pharmacies of vitamin D.[47] Whether self-medication with vitamin D has contributed to the current COVID-19 risk reduction would, therefore, be worth investigation.

VITAMIN D IN THE TREATMENT OF COVID-19 ILLNESS

Though serum 25(OH)D values >*50nmol/l* are widely associated with reduced COVID-19 risks, evidence on the use of vitamin D for treating COVID-19 has been conflicting. Initially, ever-increasing doses of cholecalciferol were given, often as repeated boluses of 1 million IU or more, without benefit. However, such doses are known not to prevent rickets as they greatly reduce vitamin D activation.[48] More modest daily dosing with cholecalciferol has now proved helpful, as has regular oral calcifediol [25(OH)D] treatment, with the added benefit that this metabolite is free of adverse effects including toxicity.[49] Meta-analyses of data from 21 randomised controlled trials [RCTs] and 8 observational studies have shown benefits in patients with 25(OH)D values below 30ng/ml [<75 nmol/l].[50] Modest doses of cholecalciferol reduced ICU admission rates in those subjects [OR=0.55, 95% CI, 0.37-0.79] in the 21 trials but significantly reduced mortality was only seen in the 8 observational studies [OR=0.45;95%CI, 0.24-0.86] and the benefits were greatest in older patients and in more severe illness.[50] A review of data on micronutrient intakes in COVID-19 reported benefits with higher intakes of agents boosting immunity [vitamins D and C] and with higher trace mineral intakes, for example of magnesium which is essential for vitamin D efficiency.[51] The benefits of calcifediol treatment in severe COVID-19 illness have also been noted to be greatest in patients not receiving steroids.[52]

Overall, therefore, adequate vitamin D provision can reduce COVID-19 risks and vitamin D treatment is a useful adjunctive measure in managing COVID-19 illness. However, whether those findings apply to dark-skinned people in the same way as has been reported for the mainly European subjects studied remains unclear.

Novel vitamin D metabolites are emerging with potential for use in COVID-19 treatment,[53] and metformin is reported to potentiate vitamin D in COVID-19 treatment, probably by improving activated vitamin D receptor signalling.[54]

Evidence to date suggests that population vitamin D status should be normalised for reduction in COVID-19 risks. Despite this, deficiency continues to be common world-wide, few governments having corrected it. Finland and northern Scandinavian countries, however, had done so with reductions in deficiency rates pre-COVID-19. It was later reported that pandemic rates of COVID-19 illness, and its mortality, were notably lower in those countries than in other Northern countries. That last observation strongly supports the likely value of improving vitamin D provision at the population level.[55] Raising serum 25(OH)D values in Black and south Asian groups by supplementation is reported

to be more effective than using food fortification. If that is confirmed, this would be important information for designing national policies for avoiding vitamin D deficiency in many countries.[56]

While anti-virals effective against COVID-19 are needed, as are effective treatments of COVID-19-induced tissue damage, treatment with vitamin D appears to be a simple and worthwhile adjunctive measure for patients whose admission serum 25(OH)D values are <30ng/ml [<75nmol/l]. Effective vitamin D treatments to data are either cholecalciferol at 100,000 IU [spread over 2 weeks], or calcifediol [25(OH)D] orally, at 0.532 mg on day 1, plus 6 doses of 0.266mg over a month. Oral calcifediol raises serum 25(OH)D levels the fastest but both these regimes can significantly reduce both the severity and mortality of COVID-19 illness.[57]

Conclusions

1. While better treatments and better protective measures against COVID-19 are needed, the evidence available [to December 2024], strongly suggests that maintaining adult serum 25(OH)D concentrations at a minimum of 50 nmol/l can reduce COVID-19 risks by about 50%, which is important for public health.

2. Convincing evidence from trials now shows that giving vitamin D, [either as cholecalciferol [D_3] at 100,000 IU over 2 weeks, or as calcifediol [25(OH)D] at ~2 mg orally over 1 month] has adjunctive benefits in managing COVID-19 illness. The fact that calcifediol has no adverse effects and is free of the risk of toxicity makes it the treatment of choice.

3. Together the global vitamin D deficiency pandemic and the evidence supporting the value of adequate vitamin D provision in COVID-19 make a cogent case for ensuring vitamin D sufficiency at the population level globally This is most urgent for dark skinned communities as they are the most severely deficient. This would be a simple & cost-effective measure. Reducing global deficiency rates should also reduce the risks from currently spreading COVID-19 variants. In the future it should also reduce the health risks of emergent viral pathogens of similar, or even greater, virulence and infectivity, especially if it is as difficult to provide effective immunisation for any new viral pathogens as it has been for COVID-19.

Conflict of Interest:

None

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None

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