Vitamin D deficiency, COVID-19 and the BAME Community

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Introduction

As deaths from COVID-19 rise in the UK, it has become clear that people from Black, Asian, and Minority Ethnic (BAME), are being affected in numbers far beyond their share of the population.[1,2,3,4] The ethnic minority population of the UK was around 13% at the time of the last census in 2011.[5] While the cause of this disparity is probably multifactorial, it may be associated with socioeconomic, cultural, or lifestyle factors, genetic predisposition, or differences in susceptibility or response to infection.[1] Possible reasons also include an increased risk of acute respiratory tract infections,[6] an increased prevalence of Vitamin D deficiency,[7] vaccination policies in their country of birth and its immune effects,[8] increased inflammatory burden, and higher prevalence of cardiovascular risk factors such as insulin resistance, diabetes and obesity than white populations.[9] The only factor which can be easily and safely modified, in the short term, being the Vitamin D deficiency.

Vitamin D

Vitamin D is mainly derived from 7-dehydrocholesterol, present in the skin, which is converted by ultraviolet light band B (UVB) to Vitamin D3 (cholecalciferol), an inactive precursor. More than 90% of Vitamin D originates from the skin and around 10% from food intake.[10]

There are two main forms of Vitamin D, Vitamin D3 (cholecalciferol) and Vitamin D2 (ergocalciferol), which is found in food and some supplements. Following the synthesis by skin or absorption from the intestines, Vitamin D is metabolically converted into 25(OH)D in the liver, and then to the active metabolite, 1,25(OH)2D (calcitriol), in the kidneys or other organs as needed.

Vitamin D was first recognised for its role in bone mineralisation and calcium regulation, with vitamin D deficiency associated with the bone disease rickets.[11] More recently, vitamin D has been reported to exert many extra-skeletal effects[12] with studies linking vitamin D status to a broad range of human health issues. Prominent amongst these is the proposed role of vitamin D in the pathophysiology of autoimmune disease, including insulin-dependent type 1 diabetes mellitus (T1D),[13] autoimmune thyroid disease,[14] multiple sclerosis (MS), inflammatory bowel disease (IBD),[15] systemic lupus erythematosus (SLE)[16] and rheumatoid arthritis (RA).[17]

Most of vitamin D's effect arises from calcitriol entering the nuclear vitamin D receptors, present in various target cells.

Vitamin D Deficiency in the UK and in BAME

The Royal Osteoporosis Society (ROS) proposes that the following pragmatic vitamin D thresholds are adopted by UK clinicians:[18]

plasma 25(OH)D <25 nmol/L is deficient.

plasma 25(OH)D of 25–50 nmol/L may be inadequate in some people.

plasma 25(OH)D >50 nmol/L is sufficient for almost the whole population.

The Department of Health and Social Care have identified the following adult groups at risk of vitamin D deficiency.[19]

- Older people, aged 65 years and over
- People who have low or no exposure to the sun, for example those who cover their skin for cultural reasons, who are housebound or who are confined indoors for long periods
- People who have darker skin, for example people of African, African-Caribbean or South Asian origin, because their bodies are not able to make as much vitamin D as required.

There is evidence to suggest that vitamin D deficiency is widespread in the UK [20,21,22,23,24] especially in the Black Afro-Caribbean, and Asian ethnic groups. In one study from an inner- city population the prevalence of vitamin D deficiency was found in 12% in Caucasians, as compared to 26 and 31% found in Black Afro-Caribbean and Asian individuals respectively.[25]

Other studies have shown even more alarming results in UK South Asian (SA) population regarding Vitamin D deficiency. With one report suggesting that this may be as high as 94% of the SA population in the winter, and 82% in the summer (18). More recent analysis of UK Biobank cohort data showed, very high prevalence of 25-hydroxyvitamin D Deficiency in n 6433 UK South Asian adults. It showed that 29% (n 2105) had 25(OH)D <15 nmol/L (very severe deficiency), 60% (n 4354) had 25(OH)D <25 nmol/L (severe deficiency) and 93% (n 6749) had 25(OH)D < 50 nmol/L (insufficiency).[26]

This high prevalence can be accounted for by several risk factors that are particular to the SA population, including poor dietary intake of vitamin D, as many SAs in the UK have a vegetarian diet, which is low in vitamin D content. The protective effect of melanin in SA skin that limits cutaneous vitamin D synthesis is also compounded by the cultural needs to cover the body amongst many SA women.[27]

The management of Vitamin D Deficiency

In a fair skinned person, 20 to 30 minutes of sunlight exposure on the face and forearms at midday is estimated to generate the equivalent of around 2000 IU of vitamin D. Two or three such exposures a week are sufficient to achieve healthy vitamin D levels in summer.

For individuals with pigmented skin and, to a lesser extent, the elderly, exposure time or frequency need to be increased twofold to 10-fold to get the same level of vitamin D synthesis as fair skinned young individuals.[28]

The Royal Osteoporosis Society recommends a maintenance therapy comprising of vitamin D in doses equivalent to 800–2,000 IU daily (occasionally up to a maximum of 4,000 IU daily), given either daily or intermittently at higher doses.[18]

Safety of Vitamin D

While documented cases of vitamin D toxicity do appear in the literature, these are rare, and invariably relate to extremely high doses taken over an extended period of time.

Toxicity is only likely to occur in chronic over dosage where hypercalcaemia could result.29 Doses above 10,000 IU/day taken for several weeks or months are frequently associated with toxicity, including documented

hypercalcaemia.[30] The European Food Safety Authority (EFSA) advises that an upper limit of 4000 IU/day is safe for adults and children >11 years of age.[31]

Vitamin D and Immunity

Vitamin D modulates innate and adaptive immunity and inflammatory cascade. Vitamin D receptors (VDR), vitamin D responsive elements (VDRE) and CYP27B1 also plays an important role in modulating the immune system.[32] Many immune cells in the human body such as monocytes, macrophages, dendritic cells, T cells, and B cells express VDR, suggesting that vitamin D may have immunomodulatory effects.

Angiotensin converting enzyme 2 (ACE2) is the host receptor for COVID-19 virus entry into intestinal and alveolar cells. Subsequent dysregulation of the renin-angiotensin system may lead to massive cytokine activation resulting in potentially fatal acute respiratory distress syndrome (ARDS). COVID-19 is caused, beside the virus virulence, by the release of pro-inflammatory cytokines.[33]

A large amount of well-established data showed antiviral effects of vitamin D, which can interfere directly with viral replication, but can also act in immunomodulatory and anti-inflammatory way.[34] The latter effect could be crucial for the assumptive beneficial effect of vitamin D, during COVID-19 infection, since it seems that COVID-19 initially uses immune evasion mechanisms, which in some patients is followed by immune hyper-reaction and cytokine storm, which is a common pathogenic mechanism of acute respiratory disease syndrome (ARDS) and systemic inflammatory response syndrome (SIRS) development.[35]

Vitamin D has been found to modulate macrophages' response, preventing them from releasing too many inflammatory cytokines and chemokines.[36]

Vitamin D and COVID-19

Randomised controlled trials of vitamin D supplementation for the prevention of acute respiratory tract infection have yielded conflicting results, but a meta-analysis of 25 randomised controlled trials including 10,933 participants showed an overall protective effect of vitamin D supplementation against acute respiratory tract infection.[7]

There have been several studies from different part of the world indicating the significance of vitamin D levels and the infection rate as well as morbidity and mortality of COVID-19 infection.

In an interesting study the mean levels of vitamin D for 20 European countries and morbidity and mortality caused by COVID-19 were acquired. It showed negative correlations between mean levels of vitamin D (average 56 mmol/L, STDEV 10.61) in each country and the number of COVID-19 cases/1 M (mean 295.95, STDEV 298.7, and mortality/1 M (mean 5.96, STDEV 15.13).[37] Vitamin D levels are severely low in the aging population especially in Spain, Italy and Switzerland. This is also the most vulnerable group of the population in relation to COVID-19.

In an observational study in Ireland it was noted that in patients with SARS-CoV-2 related pneumonia, a baseline serum 25OHD level less than 30 mmol/L was associated with a hazard ratio (HR) for intubation of 3.19 (95percent confidence interval, 1.05 to 9.7,(p=0.03).[38]

In a recently published, population based, study, from Israel, of 7,807 individuals, 782 (10.1%) were COVID-19 positive, and 7,025 (89.9%) COVID-19 negative. The mean plasma vitamin D level was significantly lower among those who tested positive than negative for COVID-19 [19.00 ng/mL (95% confidence interval [CI] 18.41-19.59) vs. 20.55 (95% CI 20.32-20.78)]. Univariate analysis demonstrated an association between low plasma 25(OH)D level and increased likelihood of COVID-19 infection [crude odds ratio (OR) of 1.58 (95% CI 1.24-2.01, p<0.001)], and of hospitalisation due to the SARS-CoV-2 virus [crude odds ratio of 2.09 (95% CI 1.01- 4.30, p<0.05)]. In multivariate analyses that controlled for demographic variables, and psychiatric and somatic disorders, the adjusted odds ratio of COVID-19 infection [1.45 (95% CI 1.08-1.95, p<0.001)], and of hospitalization due to the SARS-CoV-2 virus [1.95 (95% CI 0.98-4.845, p=0.061)] were preserved.[39]

In a recent retrospective cohort study at an urban academic medical centre in Chicago (USA), which included patients with a 25-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol level measured within 1 year before being tested for COVID-19 from March 3 to April 10, 2020 showed that, likely deficient vitamin D status was associated with increased COVID-19 risk, a finding that suggests that randomized trials may be needed to determine whether vitamin D affects COVID-19 risk. It suggested that randomized clinical trials of interventions to reduce vitamin D deficiency are needed to determine if those interventions could reduce COVID-19 incidence, including both broad population interventions and interventions among groups at increased risk of vitamin D deficiency and/or COVID-19.[40]

COVID-19 and BAME

Concerns about a possible association between ethnicity and outcome were raised, very early in the pandemic, after the first 10 doctors in the UK to die from COVID-19 were identified as being from ethnic minorities.[2] This disparity was further evident from the data, released by Office of National Statistics (ONS), on 7th May 2020, which showed that the risk of death involving the COVID-19 among some ethnic groups was significantly higher than that of those of White ethnicity. The analysis showed, that after accounting for age, Black males are 4.2 times more likely to die from a COVID-19-related death and Black females are 4.3 times more likely than White ethnicity males and females. People of Bangladeshi and Pakistani, Indian, and Mixed ethnicities also had statistically significant raised risk of death involving COVID-19 compared with those of White ethnicity.[3] Similar pattern was also seen in the data released on 19th June 2020.[41]

According to a separate UCL analysis of NHS data from hospitals in England in March and April published in Wellcome Open Research, BAME groups are around 2-3 times more likely to die with COVID-19. After adjusting for age and region, the risk of death from COVID-19 for Black African groups was 3.24 times higher than the general population, for Pakistanis was 3.29 times higher, for Bangladeshis was 2.41 times higher, for Black Caribbeans was 2.21 times higher and for Indians was 1.7 times higher.[42]

The more serious nature of the disease in BAME population was also reflected in various studies. These concerns were confirmed by observational data from the Intensive Care National Audit and Research Centre (ICNARC), showing that 33% of COVID-19 patients admitted to critical care units, were from an ethnic minority background.[4]

Public Health England (PHE) data of COVID-19, for week 32 (from 27th July to 2nd Aug.2020) shows that though for the new hospitalisations rate (lower level of care) (n=13,178) for BAME was 20%, ICU/HDU (n=4,979) admission for COVID-19 cases was over 35%, again indicating the more serious nature of disease in BAME.[43]

In another country wide UK study (n=30,693), it was found that critical care admission was more common in South Asian (odds ratio 1.28, 95% confidence interval 1.09 to 1.52), Black (1.36, 1.14 to 1.62), and Other Ethnic Minority (1.29, 1.13 to 1.47) groups compared to the White group, after adjusting for age, sex and location. This was broadly unchanged after adjustment for deprivation and comorbidities. Patterns were similar for invasive mechanical ventilation (IMV). Elevated adjusted mortality was seen in the South Asian (hazard ratio 1.19, 1.05 to 1.36) group. The conclusion drawn was that the Ethnic Minorities in hospital with COVID-19 were more likely to be admitted to critical care and receive IMV than Whites, despite similar disease severity on admission, similar duration of symptoms, and being younger with fewer comorbidities such as chronic heart disease or dementia than the White group.[44]

Lead author of the Wellcome Open Research article,[42] Dr Rob Aldridge, said in a news release: *"Our findings support an urgent need to take action to reduce the risk of death from COVID-19 for BAME groups"*.[45]

Recommendations

Since the COVID-19 outbreak, media reports and some academic publications have suggested that vitamin D supplementation (particularly high doses) could reduce the risk and severity of COVID-19. Unfortunately, no randomised controlled trial has yet been done.

A systematic review and meta-analysis[7] of randomised controlled trials (RCTs), reporting that vitamin D supplementation reduces the risk of acute respiratory tract infections (ARTI), has been widely cited as evidence to support this suggestion.

Various recommendations have been made supporting this assumption and the available data of increased infection rates and seriousness of the condition in population with low vitamin D levels, reflects this.

A recent review recommended that to reduce the risk of infection, people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D3 doses might be useful.[46]

Another recent review suggested even higher doses suggesting using vitamin D loading doses of 200,000–300,000 IU in 50,000-IU capsules to reduce the risk and severity of COVID-19.[47]

It has been recommended that all older adults, hospital inpatients, nursing home residents and other vulnerable groups (e.g. those with diabetes mellitus or compromised immune function, those with darker skin, vegetarians and vegans, those who are overweight or obese, smokers and healthcare workers) be urgently supplemented with 20-50 g/d (800 - 2000 I U) of vitamin D to enhance their resistance to COVID-19.[48]

Adrian Martineau (Institute for Population Health Sciences, Barts and The London School of Medicine and Dentistry, Queen Mary University of London) lead author of the 2017 meta-analysis,[3] is pragmatic: *"At best vitamin D deficiency will only be one of many factors involved in determining outcome of COVID-19, but it's a problem that could be corrected safely and cheaply; there is no downside to speak of, and good reason to think there might be a benefit"*.[49]

Rose Anne Kenny (Trinity College Dublin, University of Dublin, Ireland) who led the cross-sectional study into mortality and vitamin D status and is the lead investigator of the Irish Longitudinal Study on Ageing (TILDA)[50], is adamant that the recommendations from all public health bodies should be for the population to take vitamin D supplements during this pandemic. *"The circumstantial evidence is very strong"*, she proclaims regarding the potential effect on COVID-19 outcomes and adds *"we don't have randomised controlled trial evidence, but how long do you want to wait in the context of such a crisis? We know vitamin D is important for musculoskeletal function, so people should be taking it any way"*.[49]

It is also important to note that low vitamin D status may be exacerbated during this COVID-19 crisis (e.g. due to indoor living and hence reduced sun exposure), and anyone who is self-isolating with limited access to sunlight is at increased risk of vitamin D deficiency.

Further research is definitely needed to determine vitamin D deficiency factors in COVID-19 susceptibility, incidence progression and outcomes. In the face of the continuing COVID-19 epidemic, and in the absence of a vaccine or any effective anti-viral drug therapy to treat those infected, these findings call for the prioritised supplementation of all high risk adults with vitamin D at a minimum daily dose of 20-50 micrograms (800-2000 IU) per day and this advice should be quickly disseminated to the general population. Meanwhile, peoples of all ethnicities must continue hand-washing and safe hygiene, social distancing and self-isolation when required. The public should also be encouraged to maintain healthy lifestyles to optimise cardiometabolic and mental health.

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