Vitamin D Deficiency is Associated with Increased COVID-19 Severity: Prospective Screening of At-Risk Groups is Medically Indicated

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Abstract

Non-classical actions of Vitamin D are involved in regulation of the immune system including a role in mitigation of excessive inflammation. We hypothesized that vitamin D deficiency existing prior to SARS-CoV-2 infection could contribute to patients developing severe pulmonary compromise as a result of dysfunctional hyperinflammation. Serum vitamin D concentrations of patients experiencing such severe COVID-19 manifestations that they required ICU care at any point of their hospitalization were compared to serum vitamin D concentrations of patients achieving discharge without the need for any ICU care. Having serum vitamin D < 20 ng/mL was significantly associated with increased COVID-19 severity, p=0.001. It is conjectured that population groups know to have low serum vitamin D should be prospectively screened for deficiency and if found emergently treated. Such action could both decrease the maximum severity suffered by infected individuals and lessen the strain on medical resources by decreasing the percentage of COVID-19 hospital admissions requiring ICU care.

Background

SARS-CoV-2 infection (COVID-19) manifests itself on a clinical spectrum ranging from asymptomatic carriage to life-threatening disease with catastrophic compromise often due to a hyperinflammatory necrotizing pneumonitis [1,2]. African Americans, Native Americans, Hispanic Americans, obese individuals and the elderly are among groups experiencing disproportionately high levels of severe disease compared a to younger, normal Body Mass Index (BMI), Caucasian control population [3,4,5,6,7]. However, instead of attributing these discrepancies to genetic susceptibility or unavoidable effects of aging there is an evolving recognition that asymmetries of socioeconomic status , chronic stress, the availability of routine and acute medical care, and exposure to toxic environmental factors may be primarily responsible for the increased morbidity being suffered by these groups [3,8]. These same groups are also known to be disproportionately 25-hydroxyvitamin D (25VD) insufficient (serum levels of 20-30 ng/dL) or deficient (serum levels<20 ng/dL) [9,10,11]. While the etiology of the necrotizing pulmonary process is no doubt multifactorial, vitamin D deficiency has been targeted as is a candidate factor for abetting some of the dysfunctional hyperinflammation [12,13] occurring in these patients. Vitamin D deficiency affects various macrophage populations generally leading to a dampening of local production of 1,25-dihydroxyvitamin D (1,25VD), the effector molecule of intracrine, autocrine and paracrine actions of vitamin D [14]. Specifically, vitamin D deficiency has been found to increase the concentration of inflammatory mediators at the sites of viral infection while decreasing the population of adjacent regulatory T-cells [14]. This regulation of immune-mediated inflammation is partially dependent on the circulating level of 25VD, the predominant analyte measured with routine Vitamin D testing. Notable, the circulating level of 1,25VD which is mainly of renal origin and functions as the active vitamin D moiety involved in calcium homeostasis and bone health is not responsible for these in-situ actions.

CONCEPTUAL FRAMEWORK

Current therapeutic interventions for COVID-19 patients have already focused on decreasing or controlling excessive inflammation [15] but few studies have examined the role of vitamin D insufficiency as an independent factor contributing to clinical disease severity, presumably through its effect on inflammation and more broadly on the multifaceted relationship of vitamin D sufficiency with maintenance of a well-functioning immune system [16,17]. Vitamin D is also involved in neutrophil production of cathelicidins which have both anti-bacterial and anti-viral activity [18] such that decreased cathelicidin production accompanying 25VD deficiency has been proposed to increase the severity of viral and bacterial pulmonary infections [19,20]. Therefore, prompted by these physiologic and epidemiologic considerations, the possibility that deficient VD would be associated with more severe COVID-19 led us to compare 25VD levels of hospitalized COVID-19 patients requiring any days of ICU admission (a more severe "ICU" group) with the levels of COVID-19 patients able to achieve hospital discharge without the need for any ICU care (a less severe "Floor" group).

Methods

Our Biobank stores remnant EDTA plasma samples on SARS-CoV-2 PCR-positive patients. Because patient consent is obtained on hospital admission sample bias due to ordering patterns based on disease progression was not felt to be a confounding factor. Specimens for testing were randomly selected from each severity group while aiming for an approximately even split, in this case 20 ICU and 17 Floor subjects in this pilot study (N=37). Expedited IRB approval, which obviated the need for patient consent, was given to assay 25(OH)VD by standard laboratory means and collect data on sex, race, age and BMI while maintaining patient anonymity. ICU patients were comprised of 4 females and 16 males; Floor patients were 8 females and 9 males. Of the 25 men there were 17 Caucasians, 6 African Americans, and 2 Asians, and of the 12 women there were 8 Caucasians, 3 African Americans, and 1 Asian. Admissions occurred during April and May of 2020. Vitamin D deficiency was defined as 25(OH)VD<20 (ng/mL) and obesity as a Body Mass Index (BMI) >30.

Results

Race and sex were statistically similar in ICU and Floor patients. ICU patients were younger, with a mean age of 67.8 ± 10.4 v 76.4 ± 17.3 years (Wilcoxon rank sum test p=0.026). ICU patients had higher mean BMI, 28.3 ± 7.4 v 22.9 ± 4.4 (Wilcoxon p=0.017) and lower 25(OH)VD, 21.3 ± 12.2 v 32.4 ± 15.4 (Wilcoxon p=0.002). African Americans had lower mean 25(OH)VD than others, 16.8 ± 5.0 v 29.5 ± 15.4 (Wilcoxon p=0.010). Eleven of 13 (84.6%) patients with vitamin D deficiency versus 9/24 (37.5%) with adequate 25(OH)VD required ICU treatment (Fig. 1), relative risk (RR) = 2.26, 95% confidence interval (CI) = 1.28 – 3.97 (Fisher p = 0.014). A logistic regression model demonstrated that for patients having either 25(OH)VD<20 ng/mL or BMI>30, 16 of 20 ICU patients had one or both parameters versus 2 of 17 for Floor-only admission (P < 0.0001). For the same BMI, higher VD appeared protective against ICU admission with an Odds Ratio = 0.68 for a 5 ng/mL increase. For subjects with the same VD, higher BMI associated with a higher rate of ICU admission with Odds Ratio = 2.27 for a 5-unit increase in BMI.

Conclusions

Our findings strongly suggest that pre-existing VD deficiency is at least in part responsible for increased COVID-19 severity and acts synergistically with, but also independently of obesity. Graphic representation of our results are shown in Figures 1, 2, 3 and 4.

Although we are reporting on only 37 patients they were all from one institution, were admitted in a restricted time-window to limit the effect of changing therapy on disease evolution, and were under the care of a limited staff of Acute-Care/Pulmonary specialists all using the same criteria for ICU admission and the same standards-of-care for hospitalized COVID-19 patients. This uniformity of evaluation and treatment lends an added level of confidence to our statistical analysis. Our conclusion supports and expands that of a recent study by De Smet et al from Belgium [21] demonstrating that vitamin D deficiency (also using at a cut-off of 20 ng/mL) is associated with more advanced COVID-19 related pulmonary disease as determined by chest CT. Appraising our findings in conjunction with those of De Smet it is compelling to conclude that the clinically severe physiologic compromise necessitating ICU care of our 25VD deficient patients is a direct manifestation of the disease process reflected in their radiologic findings and that preexisting vitamin D deficiency is very likely an easily remediable factor contributing to increased disease severity. Additional investigation is needed to determine whether 25VD deficient patients already infected with SARS-CoV-2 would benefit from correction of their deficiency.

A recent advisory from Public Health England of 06/29/2020 [22] states there is “no evidence to support taking vitamin D supplements to specifically prevent of treat COVID-19”. The ‘Joint Statement on Vitamin D in the Era of COVID-19’ released 07/09/2020 by the Endocrine Society and five other organizations [23] stresses the need for individuals to maintain sun exposure and to supplement with 400-1000 IU of vitamin D daily. Our conclusions are not at odds with these two statements but rather addresses the need for prompt anticipatory evaluation of serum 25VD for members of groups known to be at increased risk for 25VD deficiency. Unfortunately, routine vitamin D supplementation is often ineffective [24] for older individuals such that follow-up monitoring is required to assure that sufficient serum levels are attained. This need to evaluate the outcome of supplementation should probably apply to all individuals being urgently screened for 25VD deficiency. If ongoing patient follow-up studies demonstrate that significant multi-system complications result from even mild-to-moderate COVID-19 [25,26] universal prospective vitamin D screening should become a standard component of preventative medical care.

Our recommendation is to expeditiously screen groups known to have both disproportionately high rates of severe COVID-19 relative to their population percentages and vitamin D deficiency. Up to 40% of African Americans are suspected to be vitamin D deficient at random seasonal testing [10] but this percentage that may reach 65 % in winter months [27]. Native Americans have been infrequently evaluated for their 25VD status but a report from Oklahoma found that two-thirds of apparently healthy individuals had 25VD below 20 ng/dL [9]. Nursing home residents not taking vitamin D supplementation may have a deficiency rate over 60%; even with standard supplementation up to 16% remain deficient

[28]. Profound vitamin D deficiency, though of variable percentage depending on the country of origin, has been substantiated in recent immigrants to Minnesota, Calgary, and Amsterdam [29,30,31]. Pregnant women and obese individuals are two additional population groups of concern. Evaluating healthy pregnant women from Pennsylvania in 2007 Bodnar et al [32] found 29% of black women and 5% of white women were 25VD deficient at delivery. By 2015 the obstetric situation was minimally changed: healthy women from the state of Washington, assessed at various times in pregnancy, were studied by Flood-Nichols et al [33] who found 19% of black women and 7% of white women to be vitamin D deficient. In light of an MMWR comment of 8/27/20 [34] suggesting that SARS-CoV-2 infected pregnant women "are more likely to be hospitalized and are at increased risk for ICU admission and receipt of mechanical ventilation than nonpregnant women" pregnancy does not appear to be a condition in which vitamin D deficiency should be neglected as part of routine care. Increasing obesity correlates with decreasing serum 25VD but total-body deficiency is rarely encountered due to modified distribution into differentially increased volumes of various tissues [35]. However, as mentioned in our RESULTS section, for the same BMI a higher 25VD was mildly protective of ICU admission suggesting that attempting correction of a recognized deficiency may be indicated.

NEW CONTRIBUTION to the LITERATURE

Prospective screening and remediation of vitamin D deficiency in groups at high-risk for severe COVID-19 disease is likely to attenuate an individual patient's peak physiologic compromise from subsequent SARS-CoV-2 infection. From a Public Health and medical-systems perspective the percentage of COVID-19 patients requiring ICU care would be diminished. Though relying predominantly on North American data to reach our conclusions, the testing implications apply to the many vitamin D deficient people throughout the world.

Declarations

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