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Vitamin D, COVID-19, and Cytokine Storm

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For many, the COVID-19 virus infection causes mild to moderate illness. But about 14% may require hospitalization, and about 7% require intensive care. A question for the natural practitioner is what we might offer to prevent the progression from moderate to severe disease, or to support survival in the hospitalized patient. Our normal methods with immune-enhancing, expectorant, and diaphoretic herbs may prevent progression, but we have little to offer once a patient is hospitalized or in the ICU. The answer here is not herbal for the patient headed to the ICU, but vitamin D status may be important for enhanced immunity at first infection, reduced inflammation in critical care, and reduced complications and death in the ICU. Optimal status can be obtained as prevention, or at any time during the progression of disease.

In a review article of 14 previous studies looking at consequences of vitamin D deficiency in critically ill hospitalized patients, levels of 25(OH)D3 of less than 20 ng/mL were associated with a 57% increased rate of infection, 46% increase in sepsis, in-hospital mortality was increased by 79% and 30-day mortality was increased by 76%, compared to those with level above that (de Haan et al). For perspective, the *average* vitamin D level in North American middle-aged individuals is about 28 ng/mL at the end of summer, which then plummets to about 16 ng/mL at the end of February, because of reduced wintertime sun exposure in northern temperate latitudes. This puts more than half the population at higher risk for severe complications of critical illness. These were not specifically patients with COVID-19 or influenza infection but epidemiological evidence as well a some clinical trials, suggest the importance of the seasonal "vitamin D winter" and its effect on respiratory immunity and systemic inflammation. Seasonal influenza, the SARS epidemic of 2003, and the current COVID-19 epidemic have all followed the pattern of emergence during the vitamin D winter, and improvement as sun exposure increases. This is not to downplay the heroic efforts in China and by various other governments to contain these epidemics. In one retrospective analysis of the 1918 influenza epidemic, the authors examined case fatality rates and the number of cases progressing to pneumonia in twelve locations in North America where the data was available. They then assessed the average exposure in those areas to ultraviolet light radiation in both summer and winter, in order to estimate likely vitamin D status of the population there. The authors found a very strong correlation between higher solar radiation and the likelihood that the influenza would not progress to pneumonia, and also that the patient would survive. The authors point out that correcting vitamin D deficiency up-regulates the antimicrobial immunity, at the same time reducing production of pro-inflammatory cytokines, exactly the activity to be desired in a COVID-19 patient under critical care (Grant and Giovannucci).

Another demonstration of the possible contribution of vitamin D deficiency to the excess mortality of the 1918 epidemic is the fact that the vitamin D deficiency disease Rickets was endemic in the United State in that era. Rates were much lower in 1890, but with the mass migration of a large part of the US population from the countryside to the cities over the next thirty years, Rickets became endemic in the U.S. Medical Historian Mary Weick described the statistics from the 1920's as "almost unbelievable." (Weick) Nearly 100% of babies born in Boston, New York, Washington DC, Cincinnati, and New Orleans developed Rickets by the age of one year old in 1920. One aspect of Rickets, and of vitamin D deficiency, is increased respiratory infection. These statistics suggest a population wide nearly universal vitamin D deficiency in 1918, with accompanying respiratory immuno-deficiency, and the heightened likelihood of progression to pneumonia, and reduced likelihood of recovering from severe disease.

The result of recent clinical trials of vitamin D on respiratory infection is mixed, due to different levels of vitamin D given, to baseline levels in the subject, and to outcomes measured. Trials with an adequate dose in individuals with demonstrated deficiency at baseline show a powerful reduction of frequency or severity of respiratory infections. Generally vitamin D reduces respiratory infections in those with serum levels of 25(OH)D3 below 20 ng/mL, while showing little benefit on infections for those with levels above that.

- In a trial published this month (March 2002) regular supplementation of infants between birth and six months reduced respiratory infections by more than 50%, lower respiratory tract infection, and hospitalization due to lower tract infection was reduced by about 85%. For infants not receiving vitamin D, the average time to the first RTI was 60 days. For those receiving any level of vitamin D supplementation, the time was more than six months. (Hong et al.)
- A 2017 meta-analysis if clinical trials for vitamin D supplementation and respiratory tract infections found that supplementation in those who were deficient reduced the frequency or RTI by 70% in patients who were deficient, and by 25% even in patients with officially adequate amounts. (Martineau et al).
- In a 2010 clinical trial, school children receiving a vitamin D supplement experienced a 42% reduction in the incidence of influenza A compared to those not taking it. These children also experienced a 83% reduction is asthma attacks. (Urashima et al.)

For normal prevention of the wintertime drop in vitamin D levels, and individual needs to take between 4000 IU and 7000 IU of vitamin D3 a day. It is best taken daily, and make up missed doses the next day. If an individual has not been taking vitamin D through the winter, they may assume that they are deficient. This is a very big issue to people of color in Northern or Southern temperate latitudes. When exposed to full body sunlight, a light skinned white person will make 20,000 IU of Vitamin D in 20 minutes. A very dark-skinned person will take 3 hours to make the same amount of vitamin D. People of other skin tones will fall somewhere in between. The reason is that the melanin in the skin acts as a sun block and greatly reduces exposure to the ultraviolet B rays necessary to make vitamin D. Vitamin D deficiency is much more common in dark skinned individuals. Following the above dosing takes weeks to months to restore normal levels. In the midst of a pandemic with cases increasing exponentially day by day, it may be beneficial to follow the advice of a group of vitamin D experts writing on the role of vitamin D in influenza epidemics.

> *"If the ability of vitamin D to stimulate the production of virucidal antimicrobial peptides and to suppress cytokine and chemokine production is clinically significant, then pharmacological doses(1000–2000 IU/kg per day for several days) may be useful in the treatment of those viral respiratory infections that peak in wintertime."*
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> Cannell et al.

The authors suggest this as acute treatment for symptomatic illness in patients suspected of deficiency. This translates into doses of 75,000 to 150,000 IU per day in a 165 lb individual for several days. This level is non-toxic, and for reference, throughout most of the 20th century, after the discovery of vitamin D, doses of 300,000 IU were routinely given to infants and toddlers showing signs of Rickets. Restoration of normal levels may prevent progression to more complicated illness, and may moderate any tendency to cytokine storm or morbidity if the patient ends up in the hospital.

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