LETTER TO THE EDITOR

Low Serum Levels of 25-Hydroxyvitamin D Accompany Severe COVID-19 Because it is a Negative Acute Phase Reactant

Dear Editor:

Following the onset of the COVID-19 pandemic, there has been considerable interest in the possibility that low vitamin D levels are associated with severe illness and mortality in this disease. As of today (April 27, 2021) a PubMed search for COVID-19 or SARS-COV-2 and Vitamin D yielded 567 hits. Many of these articles reported a positive association between vitamin D deficiency (based on low 25-hydroxy-vitamin D (25[OH]D) levels) and severity of disease. These findings have led to the suggestion that vitamin D be administered to COVID-19 patients to ameliorate this disease. (Indeed, vitamin D was administered to then President, Donald Trump, when he was admitted to Walter Reed Hospital with COVID-19, and even Dr. Anthony Fauci has recommended taking vitamin D supplements.) A number of randomized controlled trials are currently in progress, one of which did not support the use of a high dose of vitamin D_3 for treatment of moderate to severe COVID-19 in hospitalized patients.[1]

In fact, interpretation of serum 25[OH]D levels has been a source of considerable controversy. For skeletal health, levels >20ng/mL have been generally accepted as sufficient since the Institute of Medicine (IOM) defined this level. This estimate by a group of experts has been challenged to be far too low as well as too high. This debate may have led to over screening and unnecessary supplementation, with considerable disagreement about what levels to regard as indicating vitamin D deficiency or insufficiency. According to UpToDate, the definitions of vitamin D sufficiency, insufficiency, and deficiency are only approximate.

In addition, based on the high prevalence of low serum levels of 25[OH]D in the population, the estimated prevalence of vitamin D deficiency is felt to be surprisingly high –high enough to be dubbed *pandemic* by some authors, although this characterization has been called into question. In the National Health and Nutrition Examination Survey (NHANES), 41.6% of adult persons were found to have 25[OH]D levels below 20 ng/mL, felt to be consistent with vitamin D deficiency. It has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.

Much of this uncertainty results from the presumption that serum 25[OH]D concentrations reflect nothing but vitamin D status; but, it is becoming apparent that this is not the only explanation for low 25[OH]D levels. What has been overlooked is the abundant evidence that 25[OH]D is a component of the acute phase response, that it is a negative acute phase reactant, as others have suggested.[2,3] Just as low serum levels of albumin, a negative acute phase reactant, do not always indicate malnutrition, low 25[OH]D levels do not always indicate vitamin D deficiency. Its serum concentration decreases in response to systemic inflammation, confounding interpretation of 25[OH]D levels, and thus explaining the association of low 25[OH]D levels with severe COVID-19. It also explains the uncertainty about what level of serum 25[OH]D indicates vitamin deficiency and the presumed high prevalence of vitamin D deficiency in the population.

METABOLIC STRESS INDUCES LOW-GRADE INFLAMMATION AND AN ACUTE PHASE RESPONSE

A large number of systemic changes accompany inflammation – the acute phase response. Inflammation, one of the first responses of the activated innate immune system, has long been defined as the response to infection and tissue injury. Its presence was classically recognized by the presence of heat, swelling, redness, and pain. Inflammation is triggered by receptors which recognize pathogen-associated molecular patterns (PAMPs) in the case of microorganism-induced inflammation, and by damage-associated molecular patterns (DAMPs) in the case of tissue injury. Initial studies of the acute phase response followed on the discovery in 1930 of marked increases in concentration of C-reactive protein (CRP) in the serum of patients during the acute phase of pneumococcal pneumonia and other infectious diseases. Positive acute phase reactants are molecules whose plasma concentrations rise during the acute phase response; examples include CRP, serum amyloid A, and fibrinogen. Negative acute phase reactants, whose serum concentrations fall during inflammatory states, include albumin, transferrin, zinc, and iron, among others.[4]

In the 21st century, however, our understanding of what can elicit inflammation has expanded considerably. We have learned that the innate immune system responds to metabolic stress with chronic low-grade inflammation – "metaflammation" – without the classic signs of acute inflammation. This has led to a redefinition of inflammation as the innate immune response to harmful stimuli such as pathogens, injury and metabolic

stress.[5] Low-grade inflammation is accompanied by a modest acute phase response, including a minor degree of CRP elevation, commonly characterized today as systemic inflammation. Just beginning to be investigated are the harmful metabolic stimuli that can trigger inflammatory responses via metabolism-associated molecular patterns (MAMPs) and NLRP3.

Low-grade inflammation, as manifested by minor CRP elevation, is associated with an astounding number of conditions and lifestyles associated with poor health and that represent or reflect metabolic stresses. Examples include diabetes mellitus, obesity, hypertension, atrial fibrillation, obstructive sleep apnea, excessive nutrient consumption, poor sleep, the Western lifestyle, and a large variety of unhealthy diets.

EVIDENCE THAT VITAMIN D IS A NEGATIVE ACUTE PHASE REACTANT

The conclusion that 25[OH]D is a negative acute phase reactant is now supported by three independent lines of evidence.

1 It is well established that serum CRP and 25[OH]D levels are inversely correlated, as would be expected if 25[OH]D were a negative acute phase reactant.[6,7]
2 Low blood levels of 25[OH]D are associated with numerous medical conditions consonant with metabolic stress, including preeclampsia, autoimmune disorders, infectious diseases, cardiovascular disease, cancers, type 2 diabetes, subcutaneous and visceral adiposity and obesity, neurological disorders, acute pancreatitis, and a variety of other inflammatory states.[8,9] These findings have generally been interpreted to indicate that deficiency of vitamin D predisposes to or aggravates those conditions, rather than considering the possibility that it is the conditions themselves that lead to a low 25[OH]D level – a classic chicken and egg conundrum. Again, this would be expected if 25[OH]D were a negative acute phase reactant.
3 Most tellingly, 25(OH)D levels fall during a variety of inflammatory insults - a classic test for acute phase reactant behavior. Surgical stress, an induced inflammatory insult, may be associated with a 40% reduction in circulating 25(OH)D levels when compared to preoperative values.[2,3,10–12] Low levels of 25(OH)D persist in obese patients undergoing bariatric surgery despite various aggressive vitamin D supplementation regimens, as would be expected of a negative acute phase reactant.[13]

The recognition that 25[OH]D is a negative acute phase reactant explains the association of low 25[OH]D levels with severe COVID-19. The underling medical conditions such as diabetes and obesity known to increase the risk of severe COVID-19 are known to manifest low 25(OH)D serum levels.[14] And, the realization that 25(OH)D is a negative acute phase reactant helps explain both the confusion about what serum level should be regarded as indicating vitamin deficiency and why its prevalence in the population has been felt to be so high. About 30% of the population manifest minor CRP elevation,[15] bespeaking a high prevalence of conditions that manifest low-grade inflammation with accompanying systemic inflammation. At least some of the low levels of 25(OH)D found in the community result from its behavior as a negative acute phase reactant, leading to uncertainty about what to employ as the cutoff that indicates vitamin deficiency as well as to overestimation of the prevalence of vitamin deficiency in the community.

CLINICAL CONSIDERATIONS

Since serum concentrations of 25(OH)D decrease in the presence of systemic inflammation, they are unlikely to be a reliable measure of vitamin D status in subjects afflicted with one of the many conditions that underlie systemic inflammation. Interpretation of a low serum 25 (OH)D level depends on the clinical context and may be aided by determination of serum CRP concentration. Finding a low vitamin D level in an individual whose CRP level is not elevated supports the possibility of vitamin D deficiency. On the other hand, finding even modestly elevated CRP concentration raises the possibility that systemic inflammation underlies the depressed 25(OH)D level, as well as the possibility that both vitamin deficiency and systemic inflammation are present.

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CONFLICTS OF INTEREST

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