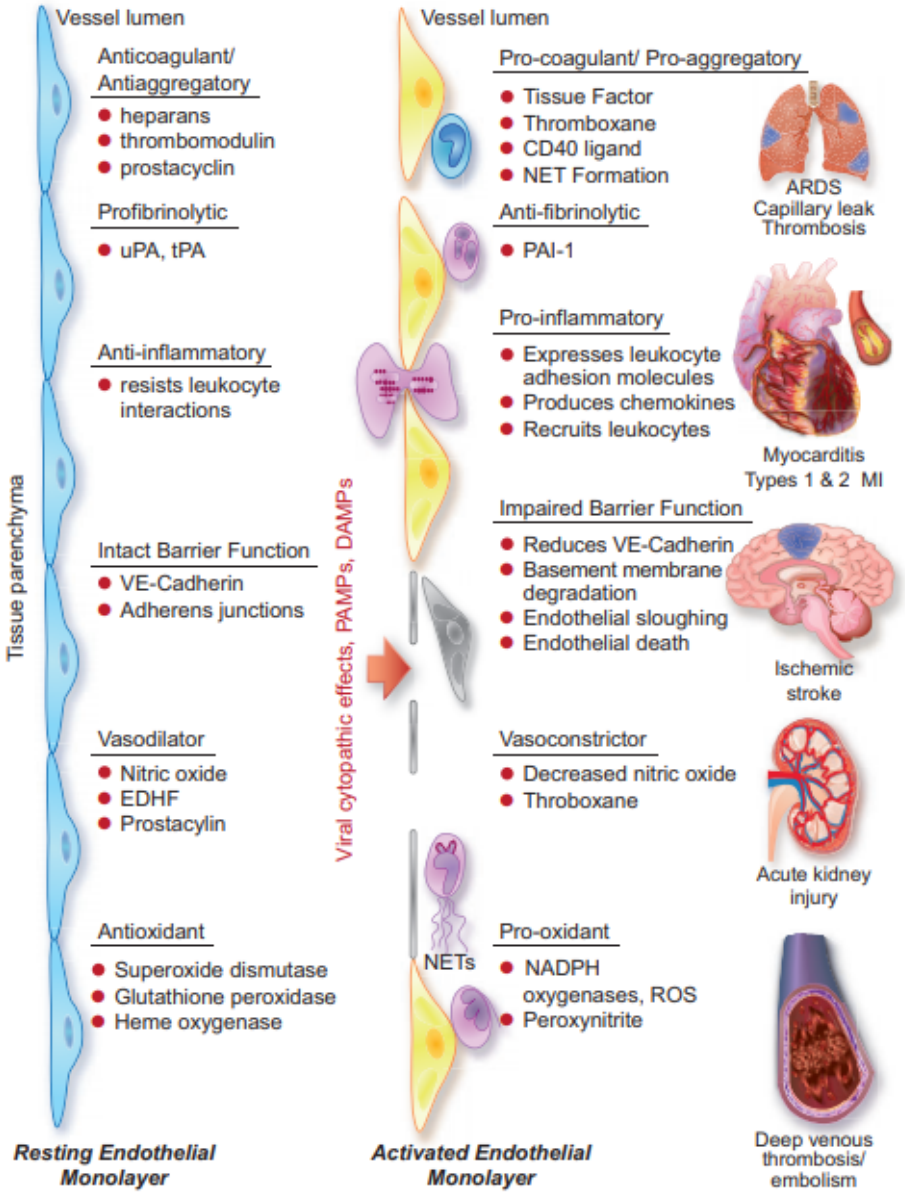
Good morning. I hope everyone had a wonderful weekend

Today I have chosen a nice review on endothelial injury and the pathogenesis of SARS-CoV-2 infection. The second article demonstrates loss of smell is more specific than loss of taste. The last 2 articles look at the role of vitamin D and SARS-CoV-2 infection. These 2 articles suggest improving vitamin D status in the general population and in particular hospitalized patients has a potential benefit in reducing the severity of morbidities and mortality associated with acquiring SARS-CoV-2.

Ed

COVID-19 Is, in the End, an Endothelial Disease
Eur Heart J published online September 3, 2020
The vascular endothelium provides an important interface between the blood compartment and tissues and displays a series of remarkable properties that normally maintain homeostasis. These tightly regulated functions include control of hemostasis, fibrinolysis, inflammation, oxidative stress, vascular permeability, and structure. While these functions participate in the moment-to-moment regulation of the circulation and coordinate many host defense mechanisms, they can also contribute to disease when their usually homeostatic and defensive functions overreact and turn against the host. SARS-CoV-2 infection can produce protean manifestations in almost all organs and at times cause significant injury to multiple organ systems including the lungs, heart, brain, kidney, intestines, and vasculature. SARS CoV-2 very much resembles an endothelial disease. Cytokines serve as key danger signals that shift endothelial functions from homeostatic into a reactive mode. The final pathway involves the “cytokine storm” which overreacts. It has been shown that cytokines like IL-1, IL-6, and TNF production increases significantly in severe SARS-CoV-2 infection. The consequences of excess cytokine production on endothelial cells include thrombosis, strokes, COVID toes (results from microvascular dysfunction), microthrombi in the lungs and other arterial beds, and venous thrombosis and pulmonary embolus. (See diagram below)



Comment: The concept of COVID-19 as an endothelial disease [discussed a few months ago in the Daily Briefing] provides a unifying pathophysiological picture and also provides a framework for a rational treatment strategy. Steroids appear to be beneficial in patients infected with SARS-CoV-2 who are oxygen dependent. Agents that inhibit IL-1 and IL-6 are under evaluation.

Seroprevalence of SARS-CoV-2 Antibodies in People with an Acute Loss in Their Sense of Smell and/or Taste in a Community-Based Population in London, UK: An Observational

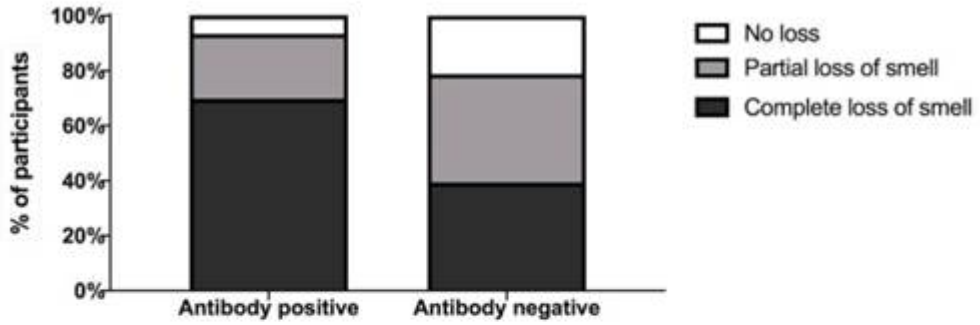
Cohort Study

PLoS Med published online October 1, 2020

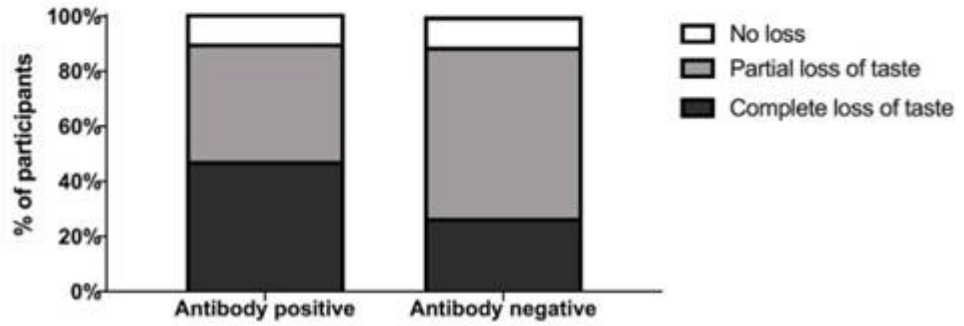
Loss of smell and taste are commonly reported symptoms associated with coronavirus disease 2019 (COVID-19); however, the seroprevalence of SARS-CoV-2 antibodies in people with acute loss of smell and/or taste is unknown. The study aimed to determine the seroprevalence of SARS-CoV-2 antibodies in a community-based population with acute loss of smell and/or taste and to compare the frequency of COVID-19 associated symptoms in participants with and without SARS-CoV-2 antibodies. It also evaluated whether smell or taste loss are indicative of COVID-19 infection.

Text messages sent via primary care centers in London invited people with loss of smell and/or taste in the preceding month, to participate. Recruitment took place between 23 April 2020 and 14 May 2020. A total of 590 participants enrolled via a web-based platform and responded to questions about loss of smell and taste and other COVID- 19–related symptoms. Mean age was 39.4 years (SD ± 12.0) and 69.1% (n = 392) of participants were female. A total of 567 (96.1%) had a telemedicine consultation during which their COVID-19–related symptoms were verified and a lateral flow immunoassay test that detected SARS-CoV-2 IgG and IgM antibodies was performed. A total of 77.6% of 567 participants with acute smell and/or taste loss had SARS-CoV-2 antibodies; of these, 39.8% (n = 175) had neither cough nor fever. New loss of smell was more prevalent in participants with SARS-CoV-2 antibodies, compared with those without antibodies (93.4% versus 78.7%, $p < 0.001$), whereas taste loss was equally prevalent (90.2% versus 89.0%, $p = 0.738$). Seropositivity for SARS-CoV-2 was 3 times more likely in participants with smell loss (OR 2.86; 95% CI 1.27–6.36; $p < 0.001$) compared with those with taste loss.

A Reported frequency of loss of smell in participants with and without SARS-CoV-2 antibodies



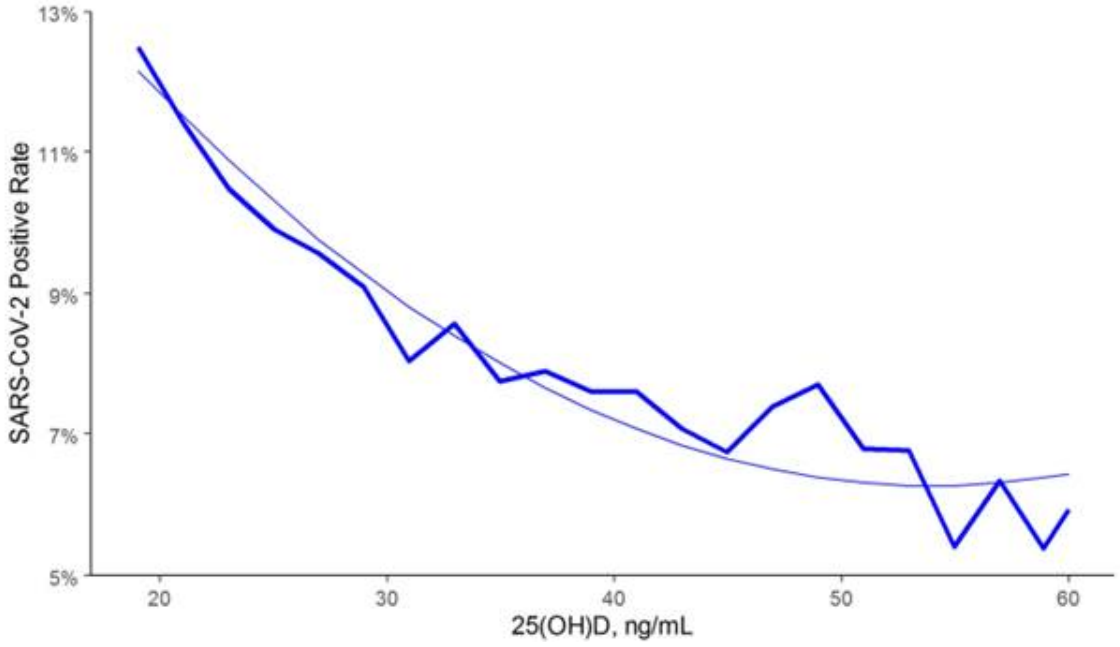
B Reported frequency of loss of taste in participants with and without SARS-CoV-2 antibodies



Comment: These findings suggest that recent loss of smell is a highly specific COVID-19 symptom and should be considered more generally in guiding case identification, isolation, testing, and perhaps treatment of COVID-19. The major limitations of this study were the lack of a general population control group and the self-reported nature of the smell and taste changes. Nonetheless this study highlights loss of smell is more specific than loss of taste and many persons with loss of smell did not have COVID-19 related symptoms.

SARS-CoV-2 Positivity Rates Associated with Circulating 25-Hydroxyvitamin D Levels
PLoS ONE published online September 17, 2020
This study used a retrospective, observational analysis of deidentified tests performed at a national clinical laboratory to determine if circulating 25-hydroxyvitamin D (25(OH)D) levels are associated with SARS-CoV-2 infection. Over 190,000 patients from all 50 states with SARS-CoV-2 results performed mid-March through mid-June 2020 and matching 25(OH)D results from the preceding 12 months were included.

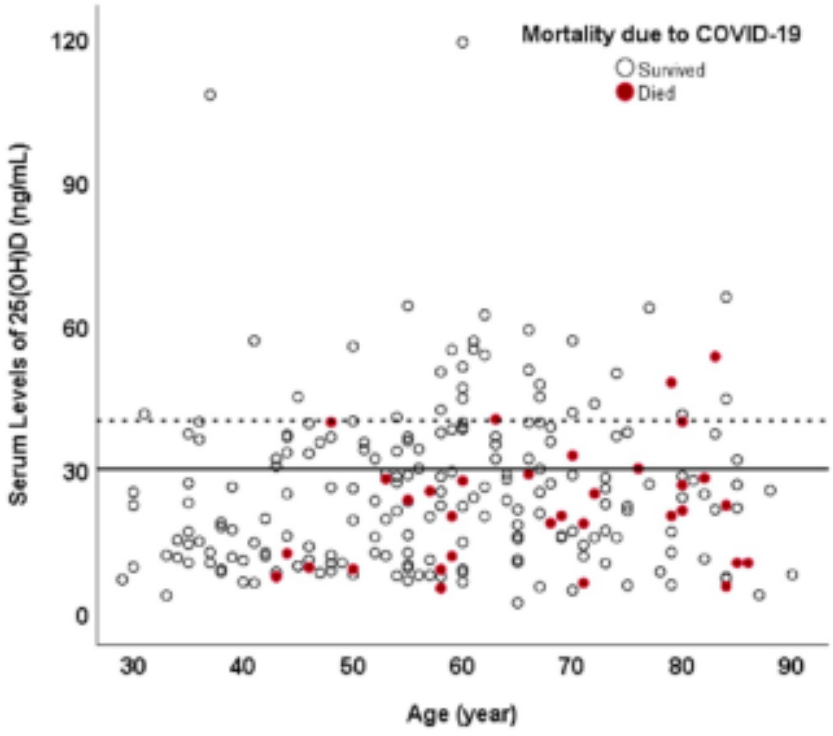
A total of 191,779 patients were included (median age, 54 years; 68% female. The SARS-CoV-2 positivity rate was 9.3% (95% C.I. 9.2–9.5%) and the mean seasonally adjusted 25(OH)D was 31.7 (SD 11.7). The SARS-CoV-2 positivity rate was higher in the 39,190 patients with "deficient" 25(OH)D values (<20 ng/mL) (12.5%, 95% C.I. 12.2–12.8%) than in the 27,870 patients with "adequate" values (30–34 ng/mL) (8.1%, 95% C.I. 7.8–8.4%) and the 12,321 patients with values ≤55 ng/mL (5.9%, 95% C.I. 5.5–6.4%). The association between 25 (OH)D levels and SARS-CoV-2 positivity was best fitted by the weighted second-order polynomial regression, which indicated strong correlation in the total population (R2 = 0.96) and in analyses stratified by all studied demographic factors. The association between lower SARS-CoV-2 positivity rates and higher circulating 25(OH)D levels remained significant in a multivariable logistic model adjusting for all included demographic factors (adjusted odds ratio 0.984 per ng/mL increment, 95% C.I. 0.983–0.986; p<0.001). SARS-CoV-2 positivity is strongly and inversely associated with circulating 25(OH)D levels, a relationship that persists across latitudes, races/ethnicities, both sexes, and age ranges.



Comment: The Daily Briefing has reviewed articles that suggested low Vitamin D may be associated with more severe SARS-CoV-2 infection. This article provides more information on the role of Vitamin D and SARS-CoV-2 and provides the **impetus** to explore whether vitamin D supplementation can reduce the risk for SARS-CoV- 2 infection and COVID-19 disease. Limitations of this study include that testing for SARS-CoV-2 was based on selection factors, including presence and significance of symptoms and exposure to infected individuals. Since this was a retrospective study there may be many other potentially confounding factors that were neither identified nor controlled for in this study. See next article

Vitamin D Sufficiency, a Serum 25- Hydroxyvitamin D at Least 30 ng/mL Reduced Risk for Adverse Clinical Outcomes in Patients with COVID-19 Infection
PLos ONE published online September 25, 2020
This study investigated the association between serum 25-hydroxyvitamin D levels and its effect on adverse clinical outcomes, and parameters of immune function and mortality due to a SARS-CoV-2 infection in hospitalized patients.

In this study population, 74% had severe COVID-19 infection and 32.8% were vitamin D sufficient. After adjusting for confounders, there was still a significant association between vitamin D sufficiency and reduction in clinical severity, inpatient mortality, lower CRP levels and an increase in lymphocyte percentage. Only 9.7% of patients older than 40 years who were vitamin D sufficient succumbed to the infection compared to 20% who had a circulating level of 25(OH)D< 30 ng/ml. The significant reduction in serum CRP along with increased lymphocytes percentage suggest that vitamin D sufficiency may have a role in modulating the immune response possibly by reducing risk for cytokine storm in response to infection.



Comment: These 2 articles suggest improving vitamin D status in the general population and in particular hospitalized patients has a potential benefit in reducing the severity of morbidities and mortality associated with acquiring COVID-19. There is a complex interaction between vitamin D, infection and the immune system. To help regulate innate immunity, 1,25(OH)2D is produced in macrophages in response to the stimulation of toll-like receptors by the binding of an infectious agent. 1,25(OH)D binds to the VDR in the macrophage resulting in an increase in the production of antimicrobial peptides (AMPs) such as defensin and cathelicidin that have antiviral effects. 1,25(OH)2D inhibits activation of B-cells and immunoglobulin synthesis. This hormone also promotes Treg cells, which are responsible for anti-infectious action by inducing IL-10 production. This leads to suppression of Th1, and Th17 cells and IFNγ, IL-17, IL-6, IL-23 and IL-2 production and makes Th2 cells predominant. Th2 cells limits inflammatory processes by inhibiting Th1 cell-mediated cytokines and TNF. Our results are very consistent with the immunomodulatory effect of vitamin D. Indeed, the anti-inflammatory role of 1,25(OH)2D could explain the protective role of vitamin D against immune hyper reaction and cytokine storm in a subgroup of patients with severe COVID-19. Studies have shown that higher CRP levels associated with vitamin D deficiency were related to an increased risk for severe COVID-19. These reports are consistent with this study. This study indicated that CRP levels in patients with higher levels of serum 25(OH)D was lower than patients with a serum level of 25(OH)D< 30 ng/mL. Also, the severity of COVID-19 infection in patients with vitamin D sufficiency was lower than other patients with higher levels of 25(OH)D. This finding supports the anti-inflammatory effect of vitamin D on reducing the inflammatory markers like CRP that was observed in this study. This anti-inflammatory effect of vitamin D might prevent cytokine storm in COVID-19 patients and may explain the decreased risk of severity and mortality observed in patients who were vitamin D sufficient. There were a few limitations in this study. First, they included patients who had recorded 25(OH)D levels. Some confounding factors, such as smoking, and social economic status were not recorded for all patients and could have a plausible impact on the COVID-19 severity. Also, the RT-PCR test was not performed on all patients with clinical signs of COVID-19. The big question moving forward, can vitamin D replacement in hospitalized patients admitted with SARS-CoV-2 infection improve outcomes who have low vitamin D levels.