Vitamin D and COVID-19
NOF ISO, May 2021

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Disclosures

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- No disclosures relevant to vitamin D

Some of this is my opinion:
Noted as such by orange text color

“With my opinion and five dollars you can get a cup of coffee.”
“For every problem there’s a solution that is simple, neat and wrong.”

H. L. Mencken
Why Are We Talking About COVID at an Osteoporosis Meeting?
Data as of May 1, 2021

For perspective – 1918 H1N1 pandemic
- 500 million infected (1/3 of world's population)
- 50 million deaths
- 675,000 in US
Why Are We Talking About COVID and Vitamin D at an Osteoporosis Meeting?

Data as of May 1, New cases and % of population with 1 dose of vaccine

With almost 1 million new infections daily and <8% of the world's population vaccinated, this will not be over soon….

If vitamin D MIGHT be of help, it is worthy of consideration
Rationale That Vitamin D Might be Important in SARS-CoV 2 Infection

- Vitamin D:
  - May have antiviral effects
  - Involved in innate immune system regulation
  - Might modulate the cytokine storm of SARS-CoV-2
  - Potential beneficial cardiovascular effects
  - Other?

Bilezikian, et. al., Eur J Endocrinol, 2020; 183: R133-R147
25 RCTs of vitamin D supplementation; 
n = 11321

Acute respiratory infection risk reduced; 
OR = 0.88

Protective effects stronger in those with 
baseline 25(OH)D < 25 nmol/L

“Vitamin D supplementation and was safe and protected against acute RTI overall. Patients very vitamin D deficient experienced the most benefit.”

Martineau, et. al., BMJ, 2017; 356:i6583, doi:10.1136/bmj.i6583

2Bergman, et. al., PLOSone, 2013: 8; e65835
Appropriate Huge Interest in Vitamin D and COVID

Selected from a Google search: vitamin D and COVID May 3, 2021
There Has Been a Worldwide Call to Increase Vitamin D

“To all governments, public health officials, doctors, and healthcare workers,
Research shows low vitamin D levels almost certainly promote COVID-19 infections, hospitalizations, and deaths. Given its safety, we call for immediate widespread increased vitamin D intakes.”

There is no need to wait for further clinical trials to increase use of something so safe, especially when remedying high rates of deficiency/insufficiency should already be a priority.”

https://vitamind4all.org/letter.pdf
This Worldwide Call States: Specifically to:

1. Recommend amounts from all sources sufficient to achieve 25(OH)D serum levels over 30 ng/mL (75 nmol/L), a widely endorsed minimum with evidence of reduced COVID-19 risk.

2. Recommend to adults vitamin D intake of 4000 IU (100 mcg) daily (or at least 2000 IU) in the absence of testing. 4000 IU is widely regarded as safe.

3. Recommend that adults at increased risk of deficiency due to excess weight, dark skin, or living in care homes may need higher intakes (e.g., 2x). Testing can help to avoid levels too low or high.

4. Recommend that adults not already receiving the above amounts get 10,000 IU (250 mcg) daily for 2-3 weeks (or until achieving 30 ng/mL if testing), followed by the daily amount above. This practice is widely regarded as safe.

5. Measure 25(OH)D levels of all hospitalized COVID-19 patients & treat w/ calcifediol or D₃, to at least remedy insufficiency <30 ng/ml (75 nmol/L)…”

https://vitamind4all.org/letter.pdf
Scientific Literature: HUGE Number of Publications on Vitamin D and COVID

- **Vitamin D**
  - 2020: 5,432 (~15/day)
  - 2021: 2220 (~18/day)

- **COVID**
  - 2020: 87,796 (~241/day)
  - 2021: 49,037 (~399/day)

I have not attempted to review everything and have doubtlessly missed and/or will not comment upon important works.

Source: Pubmed (accessed May 3, 2021)
Many Publications Review the Physiologic Rationale Behind a Vitamin D and COVID Relationship

“…apply our current understanding of vitamin D as a facilitator of immunocompetence both with regard to innate and adaptive immunity and to consider how this may relate to COVID-19 disease. There are also intriguing potential links to vitamin D as a factor in the cytokine storm…”

Bilezikian, et. al., Eur J Endocrinol, 2020; 183: R133-R147
Evidence supporting vitamin D in reducing COVID risk includes:

- Outbreak occurred in winter, when 25(OH)D lowest
- Number of cases in the Southern Hemisphere near the end of summer are low
- Vitamin D deficiency contributes to acute respiratory distress syndrome
- Case-fatality rates increase with age and with chronic disease comorbidity, which are associated with lower 25(OH)D

“To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/day of vitamin D$_3$ for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/day. 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 D$_3$ doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations.”

Grant, et. al., Nutrients 2020, 12, 988; doi:10.3390/nu12040988
A Fair Number Are Commentaries/Editorials

“Owing to the lack of specific treatment and urgency to act, these findings could be tentatively extrapolated to SARS-CoV-2 infection, justifying the use of vitamin D as a possible adjuvant therapy. From the public health aspect, the recommendation of intensive supplementation as possible prophylaxis also could be considered. Given the good tolerability and safety of even high doses of vitamin D, this approach complies with primum non nocere principle.”

Some Editorials Urge Caution

“Given that vitamin D deficiency or insufficiency are highly prevalent globally, there is no harm in recommending optimal sunlight exposure or vitamin D supplementation to the general public….”

“However, it may be premature to make any claims on the indication of vitamin D for COVID-19. Blind faith in taking vitamin D to prevent COVID-19 may give a false sense of invulnerability and increase the risk of infection and delay seeking medical diagnosis and treatment.”

Cheung and Cheung, Postgrad Med J 2021, http://dx.doi.org/10.1136/postgradmedj-2020-139388
Systematic Reviews Have Explored the Relationship of 25(OH)D With COVID

- Systematic review of 9 studies involving over 1 million participants
- “Low vitamin D levels” were correlated with COVID-19 infection, seriousness and mortality

- Systematic review of 10 studies involving ~360,000 participants
- COVID-19 positive individuals had lower vitamin D levels than negative individuals
  Liu, et. al, Int J Infect Dis 2021:104 58-64

Forrest plot of “serum vitamin D levels” in those with or without COVID-19
Low 25(OH)D is Associated With Higher Mortality

- Retrospective observational study of 186 patients with severe acute respiratory distress who had chest CT and 25(OH)D
- 59% were D deficient (based on 25(OH)D <20 ng/mL) on admission
- Vitamin D deficiency was associated with mortality independent of age, chronic lung disease and extent of lung damage on chest CT

“Our study shows an association between vitamin D deficiency and mortality of COVID-19 pneumonia and makes a call for general avoidance of vitamin D deficiency as a safe and inexpensive possible mitigation of the pandemic.”

Be Cautious With Sensational Headlines

“What is not clear is whether vitamin D levels are acting as an acute-phase reactant, dropping because of the infection with larger drops indicating more severe disease, or whether vitamin D deficiency is causing worse outcomes.”

Clinical Endocrinology News, V 16, #1, Jan 2021
Low 25(OH)D is Associated With LOWER Mortality

- 129 consecutive COVID-19 patients admitted to an Italian hospital
- 25(OH)D measured within 48 hours of admission
  - Normal ≥ 30, insufficient 20-30, moderately deficient 10-20, severely deficient < 10 ng/mL: 90% < 30 ng/mL
- Outcomes: severe pneumonia, admission to ICU, mortality and markers of disease severity, e.g., CRP
- 26% mortality; 25(OH)D not associated with clinical outcomes

“Unexpectedly, after adjusting for major confounders (age, sex, CRP, heart disease and severe pneumonia), a significant positive association between increasing 25(OH)D levels and in-hospital mortality was observed.”

Adding 25(OH)D to “Best Available Treatment”

- 76 consecutive patients hospitalized at a Univ Hosp in Spain with COVID-19 pneumonia on x-ray and positive SARS-CoV-2 PCR
- All received hydroxychloroquine and azithromycin
- Eligible patients calcifediol or not; 2:1 on day of admission
- Oral calcifediol 0.532 mg on admission; 0.266 mg on day 3 and 7 then weekly vs. nothing until discharge or ICU admission
- Outcomes: rate of ICU admission and death
- **50 treated with calcifediol, 1 (2%) admitted to ICU and no deaths vs. 13/26 (50%) untreated and 2 deaths**
- Limitations: not double blind or placebo controlled, small number
- “….calcifediol administration may improve clinical outcome of subjects requiring hospitalization for COVID-19.”

Vitamin D Reduced Inpatient Mortality

- Observational study: UK COVID inpatients; 444 initial 541 validation
- Received various cholecalciferol regimens: generally 4000-5000 IU daily or 20,000-50,000 weekly
- Primary outcome measure = COVID-19 mortality

“...cholecalciferol booster therapy, regardless of baseline 25(OH)D, appears to be associated with a reduced risk of mortality in inpatients with COVID-19.”

Ling, et. al., Nutrients, 2020, 12, 3799; doi:10.3390/nu12123799
Vitamin D Had No Effect in Hospitalized Patients

- Two site, double blind RCT in Brazil: 240 hospitalized with moderate to severe COVID
- Received **cholecalciferol 200,000 IU orally once or placebo**
- Primary outcome measure = Hospital length of stay

"The findings do not support the use of a high dose of vitamin D₃ for treatment of moderate to severe COVID-19."

Potential Conclusions

- Vitamin D deficiency/insufficiency is common worldwide
- 25(OH)D is often low in people infected with SARS-CoV2
- Vitamin D deficiency might be related to the pathophysiology of COVID
- Some reports that D administration improves outcomes
- We don’t have great drugs to cure COVID
- This is a pandemic like none of us have every seen
- *Give everybody vitamin D*
Be Cautious When Drawing Conclusions About Measured “Low” 25(OH)D Levels in COVID Patients

Personal opinion

There is a Lot to Think About Regarding the Relationship of Vitamin D With COVID (AND with Osteoporosis/Fractures)

I Don’t Know the “Right” Answer

Things to Consider…..
Challenges That Have Plagued the Vitamin D Field Remain in Effect for COVID

- Association does not prove causation
- How to define “low?”
  - Acute illness/surgery/Inflammation lowers 25(OH)D
- If 25(OH)D is indeed the correct test to define “low vitamin D status, it is necessary to report standardized data
- Vitamin D is likely a nutrient, not a drug; more is unlikely to be better and supplementing/treating vitamin D replete subjects may well have no effect

Personal opinion
We Need to be Reporting Standardized 25(OH)D Results

“25(OH)D” ≠ “25(OH)D”

Various studies reporting “25(OH)D” will include those with different vitamin D status based upon assay used

Unpublished data; manuscript submitted
Even if All Studies Immediately Started Reporting Standardized 25(OH)D Values in COVID Patients…

Do We Know What a “Low” 25(OH)D Means??
Low 25(OH)D May be DUE TO Inflammation

- Mechanism(s) unclear
- Essential to consider in all studies of acutely ill patients with COVID

Mean decrease = 28%

- Worthy of consideration….
- Is this only an assay effect OR are these people truly vitamin D deficient?
- Said another way; are low measured 25(OH)D levels truly indicative of tissue/cellular level vitamin D inadequacy?

“The metabolic meaning and the functional importance of these changes are unknown.” “…. 25(OH)D measured during acute-phase response should be interpreted with care.”

Mechanism(s) unclear
Essential to consider in all studies of acutely ill patients with COVID

Low 25(OH)D May be DUE TO Inflammation

Silva and Furlanetto, Nutr Rev, 2015; 35: 91-96
Acute Illness Lowers 25(OH)D and DBP

Surgery acutely lowers 25(OH)D; Total hip arthroplasty (n = 40)

Mean decrease ~ 8 ng/mL in 1 day

Mean decrease 7.6 ng/mL (22%)

Does this occur in just a few patients, thus affecting the mean?

Binkley, et al., Osteoporos Int, 2017; 28: 1013-1020
25(OH)D and DBP Decline In Virtually All Patients with Total Hip Arthroplasty

Acute Inflammation Lowers 25(OH)D

“Our data reveal that systemic inflammation lowers circulating 25(OH)D levels in humans. This mechanism may contribute to the low circulating 25(OH)D concentrations observed in patients suffering from infectious diseases, including COVID-19. In virtually all of these patients, onset of disease precedes hospital admission by at least several days. Our results show that 25(OH)D levels decrease within hours of initiation of a systemic inflammatory response. As such, the developing inflammatory response in COVID-19 patients may have decreased 25(OH)D before in-hospital measurements were performed.”

This Confounds ALL Reports of Low 25(OH) in COVID Patients

“These folks are amazingly sick (as sick as I have ever seen)....”

D. Coursin, M.D.
Additionally, We Should Ask:  
Is “Vitamin D” a Nutrient or a Drug?  
I’d be OK Using it as a Drug, But We Need to Recognize that is What We are Doing…..  

Personal opinion
IF Vitamin D is a Nutrient, We Should Listen to Heaney’s Advice....

- “…If the basal status is deficient, then an increase in intake will usually produce a measurable benefit.
- If the nutritional status is replete, an increase in intake will usually produce a null effect,
- and if the nutritional status is high, an increase in intake might be expected to increase risk of toxicity.”

“This point is so obvious from simple inspection of the curve that one should have thought it would go without saying.”

Heaney RP, Nutr Reviews 2013, 72:48-54
Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength
A Randomized Clinical Trial

- 3 year RCT
- 311 community dwelling adults
- Daily vitamin D$_3$; 400, 4000 or 10000 IU
- Baseline 25(OH)D respectively: 31.4, 32.5, 30.7 ng/mL

“At trial end, radial vBMD was lower for the 4,000 and 10,000 IU dose group....”
Burt, et. al., JAMA, 2019, 322: 736-745

“... if the nutritional status is high, an increase in intake might be expected to increase risk of toxicity.”
Heaney RP, Nutr Reviews 2013, 72:48-54
76 consecutive patients hospitalized at a Univ Hosp in Spain with COVID-19 pneumonia on x-ray and positive SARS-CoV-2 PCR
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Limitations: not double blind or placebo controlled, small number
“….calcifediol administration may improve clinical outcome of subjects requiring hospitalization for COVID-19.”

Castillo, et. al., J Steroid Biochm Mol Biol, 2020, 203: 105751
Even IF Vitamin D Has an Immunomodulatory Effect in COVID Infection, Could Any Such Effect be Observed Given That:

1. Patients are REALLY sick by the time they get to the hospital
   Has the horse left the barn?

2. Dexamethasone is standard treatment
   Can anything produce a more profound anti-inflammatory effect?
Does an Illness/Inflammation Induced Drop in Circulating 25(OH)D Translate to Tissue/Cellular Level Vitamin D Deficiency?

Well Designed and Thoughtful RCTs Are Needed to Clarify What Role, If Any, Vitamin D Deficiency Plays in COVID Infection and Outcomes
Many Clinical Trials are Ongoing
ClinicalTrials.gov: COVID19 & vitamin D yielded 93 studies on May 3, 2021

<table>
<thead>
<tr>
<th>Row</th>
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| 1   |       | Completed | Impact of Vitamin D Level and Supplement on SLE Patients During COVID-19 Pandemic | Covid19 | • Drug: Vitamin D  
• Diagnostic Test: ELISA | • Mansoura University Hospital  
Mansoura, DK, Egypt |
| 2   |       | Recruiting | N-terminal Pro B-type Natriuretic Peptide and Vitamin D Levels as Prognostic Markers in COVID-19 Pneumonia | COVID19 Pneumonia | • Other: Pro BNP, Vitamin D | • Kasr Alainy Cairo University  
Cairo, Giza, Egypt |
| 3   |       | Recruiting | Vitamin D and COVID-19 Trial | COVID-19 | • Dietary Supplement: vitamin D  
• Dietary Supplement: Placebo | • Brigham and Women's Hospital  
Boston, Massachusetts |
| 7   |       | Recruiting | Prevention of COVID-19 With Oral Vitamin D Supplementation Therapy In Essential healthCare Teams | COVID-19 | • Dietary Supplement: Placebo  
• Dietary Supplement: Vitamin D | • CHUM  
Montreal, Quebec, Canada  
• CHU Sainte-Justine  
Montreal, Quebec, Canada |

Huge dose range and varying dosing schedules
From 400 IU daily, through a bolus of 50,000 or 100,000 IU followed by weekly or daily to as high as 500,000 IU once
Is “Vitamin D” a Nutrient or a Drug?

Recognize that some studies (two selected examples) are using non-physiologic, i.e., pharmacologic doses

- “CARED-Trial” protocol; RCT in Argentina of hospitalized SARS-CoV-2 patients with O$_2$ sat ≥ 90%
- Intervention one dose of vitamin D$_3$, 500,000 IU or placebo
- Primary outcome is change in respiratory sepsis-related organ failure assessment score

Mariani, et. al., Trials, 2021; 22: 111

- 91 consecutive patients admitted with COVID
- ”Supplemented” with 400,000 IU D$_3$ based on physician decision
- Composite outcome of death or ICU transfer reduced by 43%
  - OR 0.57 (0.214-1.34); p = 0.20

The Human Clinical Trials Are Going to be a Mixture of Supplementation and Massive Pharmacological Doses

Additionally, a “COVID patient” Can Have Radically Differing Degrees of Illness from Asymptomatic to Lethal
Perhaps Animal Studies Could Provide Rigorously Controlled Data Assessing the Potential Importance, or Lack Thereof, for COVID Patients

Review
Animal models for influenza virus pathogenesis, transmission, and immunology
Rajagowthamee R. Thangavel a, Nicole M. Bouvier a,b,*

“Animal models are used in influenza research not only to elucidate the viral and host factors that affect influenza disease outcomes in and spread among susceptible hosts, but also to evaluate interventions designed to prevent or reduce influenza morbidity and mortality in man.”

Thangavel and Bouvier, J Immunol Methods, 2014, 410: 60-79
“For an animal to be a model for a disease, the pathogen should be able to infect the animal using the same receptor on cell used in humans and then multiply inside the host successfully. Additionally, it should provide similar clinical symptoms as humans....”

- Ferrets; increase body temperature but not other symptoms
- Mice; not infected due to differing ACE2 receptor
- Syrian hamster; weight loss and high viral load in respiratory tract
- Rhesus macaques
Respiratory disease in rhesus macaques inoculated with SARS-CoV-2

- Inoculated 8 adult rhesus monkeys with SARS-CoV-2
- Day 1; decreased appetite, fever, cough, tachypnea
- All recovered in 9-17 days
- Pulmonary infiltrates in all
- High viral load in lungs in all

“Together, our rhesus-macaque model recapitulates COVID-19 in humans with regard to virus replication and shedding, the presence of pulmonary infiltrates, histological lesions and seroconversion.”

Not Sure That this is Important, But…..
Rhesus Monkeys Have **HIGH** 25(OH)D Levels

- 25 adult rhesus laboratory raised animals

Not easy, not quick, not cheap, but……
Perhaps non-human primates could be the ideal animal model to study vitamin D and other interventions for COVID disease??

Could a Monkey Study Provide The Answers??

- Three groups
  - Vitamin D more than sufficient (usual diet)
  - Vitamin D deficient (this would take a while)
  - Pharmacologic dose daily

- Multiple outcomes could be measured
  - Cytokines
  - Radiographs
  - Viral load
  - Etc, etc

Personal opinion
Is There An Answer to the Question: Is Vitamin D Deficiency Important in SARS-CoV-2 Infection?

I’m Not Sure…

But I Suspect That Low 25(OH)D Values In Hospitalized COVID Patients Identify People With Severe Disease

Personal opinion
Dr. Michael Ryan, WHO Executive Director: “Be fast, have no regrets. The virus will always get you if you don’t move quickly; if you need to be right before you move, you will never win.” “Perfection is the enemy of the good when it comes to emergency management. The problem in society we have at the moment is that everyone is afraid of making a mistake. But the greatest error is not to move. The greatest error is to be paralysed by the fear of failure.”

- Vitamin D deficiency is common across all age groups
- We recommend daily supplementation with 800-1000 IU D₃ for most of the adult population in Ireland for duration of the pandemic
- For vulnerable groups (obese, dark skin, older, NH residents) higher doses will likely be required to achieve > 50 nmol/L
  - This should be prescribed and monitored under medical supervision

I see no downside to daily vitamin D supplementation (800-2,000 IU) to maintain a 25(OH)D level of 30-40 ng/mL, BUT…..

Doing so does not replace social distancing, masking, hand washing and vaccination

Personal opinion
Thank You