



Vitamin D - Time to end the panacea? An evidence base approach

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PRESS RELEASE

Study finds over 80 percent of COVID-19 patients have vitamin D deficiency

Washington, DC | October 27, 2020

Vitamin D deficiency was more prevalent in men

Over 80 percent of 200 COVID-19 patients in a hospital in Spain have vitamin D deficiency, according to a new study published in the Endocrine Society's *Journal of Clinical Endocrinology & Metabolism*.

HEALTH AND WELLNESS

The supplement Dr. Fauci takes to help keep his immune system healthy

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Objectives

- Role of Vit D - skeletal and extra skeletal
- Defining Vitamin D deficiency
- Common causes of Vit D deficiency and its prevention
- Who should screening? Should it be a part of our routine health maintenance?
- Treatment and work up of patients with low Vitamin D
- Toxicity of Vitamin D
- What is the evidence?
- Vit D levels and COVID-19

A little bit of history



Rickets became common in Europe in the 1700s as people began to stay indoors and live in large cities with reduced exposure to sunlight.

Cod Liver oil was first prescribed for treatment of rickets in 1824, it was known to have high Vit A. The cause: diminished intake of an ***antirachitic factor***

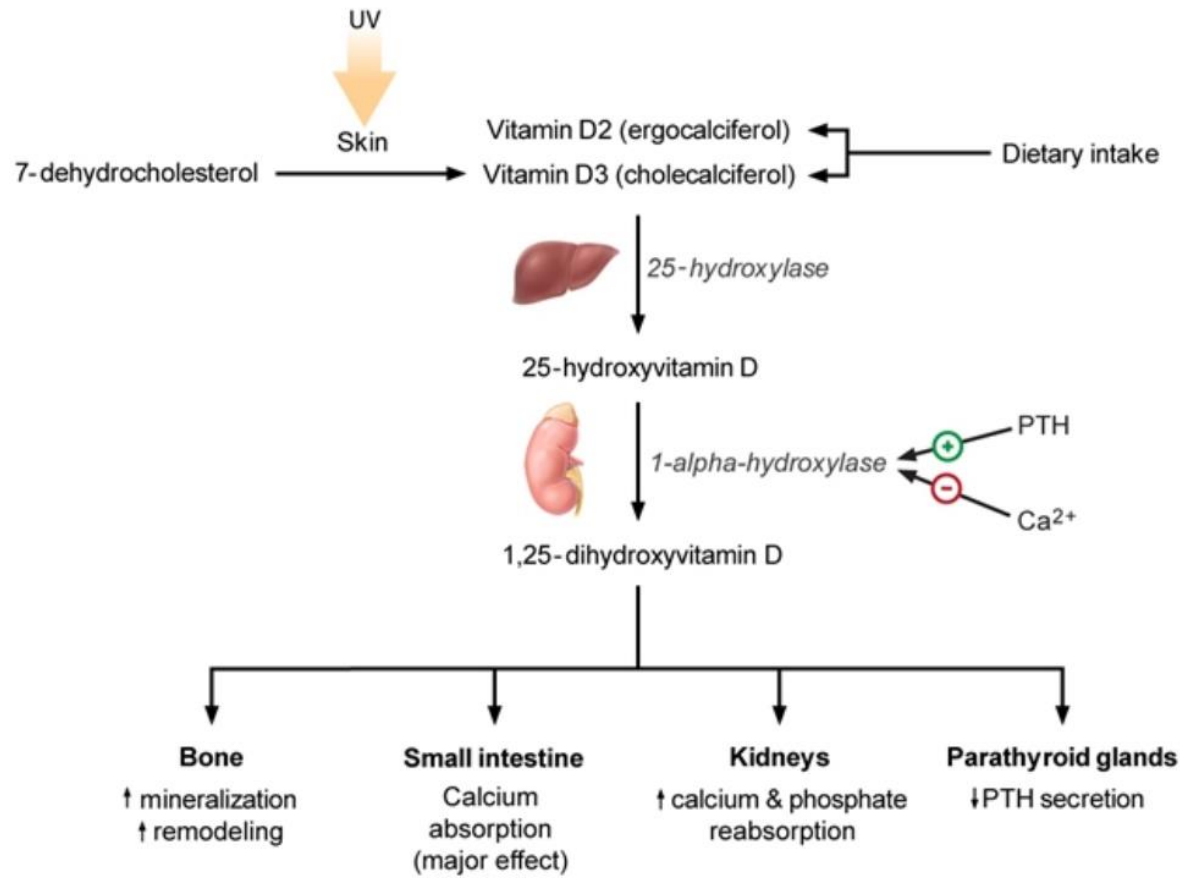
Dr. McCollum and his team from John Hopkins tried multiple oxidized fats which destroyed Vitamin A content- fish liver oils, vegetable oils, and butter fat. The only one successfully treating rickets was fish liver oil.

The newly discovered **anti-rachitic substance** was the fourth, hence was called vitamin D

Clinical observations in 1921 noted that sunlight would cure rickets just as well as cod-liver oil and there was a “seasonal incidence of rickets”

The public health prevention initiative of fortification of milk with vitamin D led to very low rates of rickets in the United States.

How is Vitamin D produced in the body?



- Fat- soluble vitamin (along with A, E, K)
- UV-B induced production of vitamin D in the skin accounts for 80%
- Few foods naturally contain Vit D (fatty fish)
- Undergoes two hydroxylations in the body for activation
- 25-(OH) D half life 3-4 weeks → **testing deficiency**
- 1,25(OH)D active vitamin D half life of 4- 6 hrs, dependent of metabolism (PTH), phosphate
- Without vitamin D, only ~ 15% of dietary Ca and ~ 60% of Phos are absorbed.

Extra skeletal functions of Vitamin D

The vitamin D receptor is present in most tissues and cells in the body

1,25(OH)₂D has a wide range of biological actions:

- *Inhibiting cellular proliferation and inducing terminal differentiation (keratinocytes – use in psoriasis)*
- *Inhibiting angiogenesis*
- *Stimulating insulin production*
- *Inhibiting renin production*
- *Stimulating macrophage activation*

May be responsible for regulating up to 200 genes encoding proteins that regulate proliferation, differentiation, and apoptosis



Vitamin D in numbers

Vitamin D supplement consumption increased 4 times in the past decade

In 2014, vitamin D levels was the fifth most common laboratory test ordered for Medicare patients, with a total cost of \$323 million/year

Ambulatory visits using the code vitamin D deficiency more than tripled between 2008 and 2010

Study in JAMA 2017 showed American (39,000 participants) are consuming more vitamin D over the time period of 1999-2014.

----Consumption of 1000IU per day rose from 0.3% to 18%



Vitamin D in numbers

TABLE 1. Prevalence of Vitamin D Deficiency in Commonly Encountered Clinical Patient Populations

| | |
|---|---------|
| Nursing home or housebound residents; mean age, 81 y | 25%-50% |
| Elderly ambulatory women, aged >80 y | 44% |
| Women with osteoporosis, aged 70-79 y | 30% |
| Patients with hip fractures; mean age, 77 y | 23% |
| African American women, aged 15-49 y | 42% |
| Adult hospitalized patients; mean age, 62 y | 57% |

National Health and Nutrition Examination Survey (NHANES) data from 2005- 2006 overall prevalence rate of vitamin D deficiency among U.S. adults was **41.6%**. The highest rate was seen in blacks (**82.1%**), followed by Hispanics (**69.2%**).

Who is at risk for Vitamin D deficiency?

- **Reduced exposure to sunlight** - the main cause of Vit D deficiency (shift workers, nursing home patients, dressing habit, skin cancer survivors)

*UVB radiation does not penetrate glass

- Darker skin - natural sun protection and require 3-5x longer exposure to make the same amount of vitamin D
- Obesity - sequestration of vitamin D in body fat
- Age - reduced 7-dehydrocholesterol in the skin (synthesis is reduced in 75% in a 70-year-old)
- Wearing a sunscreen- reduces vitamin D synthesis in the skin by more than 95%

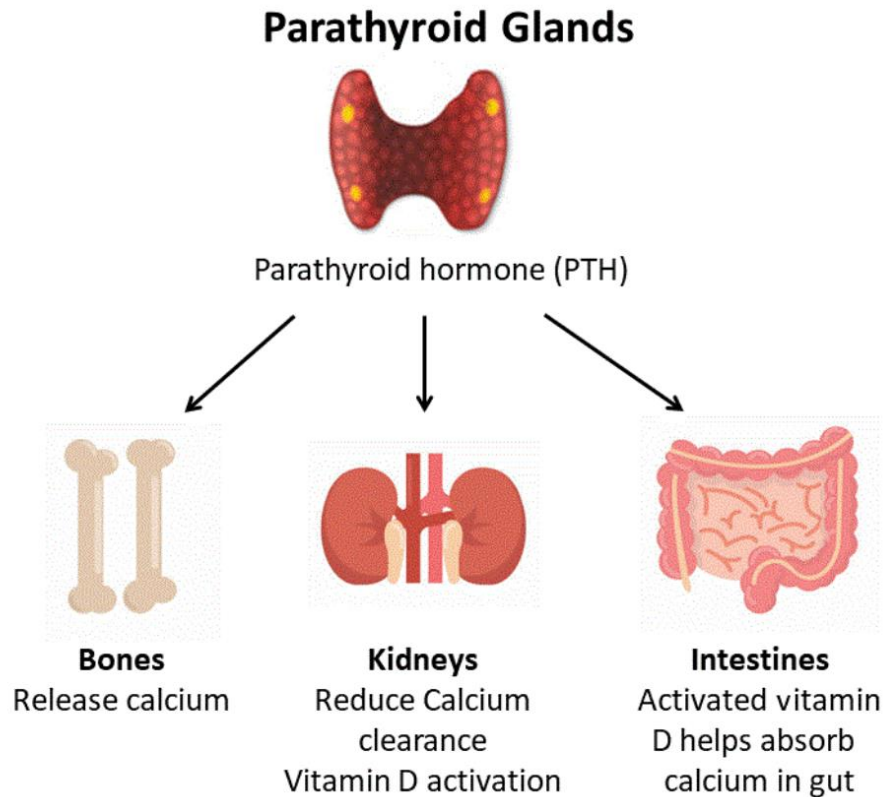


Who is at risk for Vitamin D deficiency?

- Season, latitude, and time of day - above about 35 degrees north latitude (Atlanta), little Vit D can be produced from November to February
- Liver disease - lower vitamin D binding protein
- Kidney disease - nephrotic syndrome, CKD decreased synthesis of 1,25(OH)D
- Fat malabsorption- celiac disease, Crohn disease, pancreatic insufficiency, cystic fibrosis, short gut syndrome, and cholestatic liver disease
- Chronic granuloma-forming disorders, some lymphomas, and primary hyperparathyroidism
- Breastfeeding infants - low Vit D in human milk. Depends on mothers Vit D state
- Medications: glucocorticoids, seizure medications, antifungals, cholestyramine



What are the consequences of low Vitamin D ?



Decrease in the efficiency of intestinal calcium and phosphorus absorption → increase in PTH levels

Secondary hyperparathyroidism → mobilizes calcium from bones, increasing phosphorous wasting at the kidneys.

PTH-mediated → increase in osteoclastic activity → decrease in bone mineral density (BMD), resulting in osteopenia and osteoporosis

Phosphaturia → results in an inadequate calcium-phosphorus product, causing a mineralization defect in the skeleton

What are the consequences of low Vitamin D ?

TABLE 1 Biochemical Manifestations of Different Stages of Vitamin D Deficiency

| | Plasma Ca ⁺⁺ | Plasma PO ₄ | ALP | PTH | 25(OH)-D | 1,25(OH) ₂ -D | Radiograph Changes |
|----------|-------------------------|------------------------|-----|-----|----------|--------------------------|---------------------|
| Early | N/↓ | N/↓ | ↑ | ↑ | ↓ | N | Osteopenia |
| Moderate | N/↓ | ↓ | ↑↑ | ↑↑ | ↓↓ | ↑ | Rachitic changes + |
| Severe | ↓↓ | ↓↓ | ↑↑↑ | ↑↑↑ | ↓↓↓ | ↑/N/↓ | Rachitic changes ++ |

N indicates normal; ↑, increase; ↓, decrease. + mild changes, ++ moderate to severe changes

Adapted with permission from Levine M, Zapalowski C, Kappy M. Disorders of calcium, phosphate, PTH and vitamin D metabolism. In: Kappy MS, Allen DB, Geffner ME, eds. *Principles and Practice of Pediatric Endocrinology*. Springfield, IL: Charles C. Thomas Co; 2005:762.

Normal – low Ca levels, low Vit D (<10), high PTH and low Phos

Important to remember that osteoporosis you would not find these changes

What are the consequences of low Vitamin D ?

Rickets (Children)

Defective mineralization → soften bones and skeletal deformities. Failure to thrive, developmental delay, hypocalcemic seizures, tetanic spasms, cardiomyopathy, and dental abnormalities. Difficulty standing and walking.



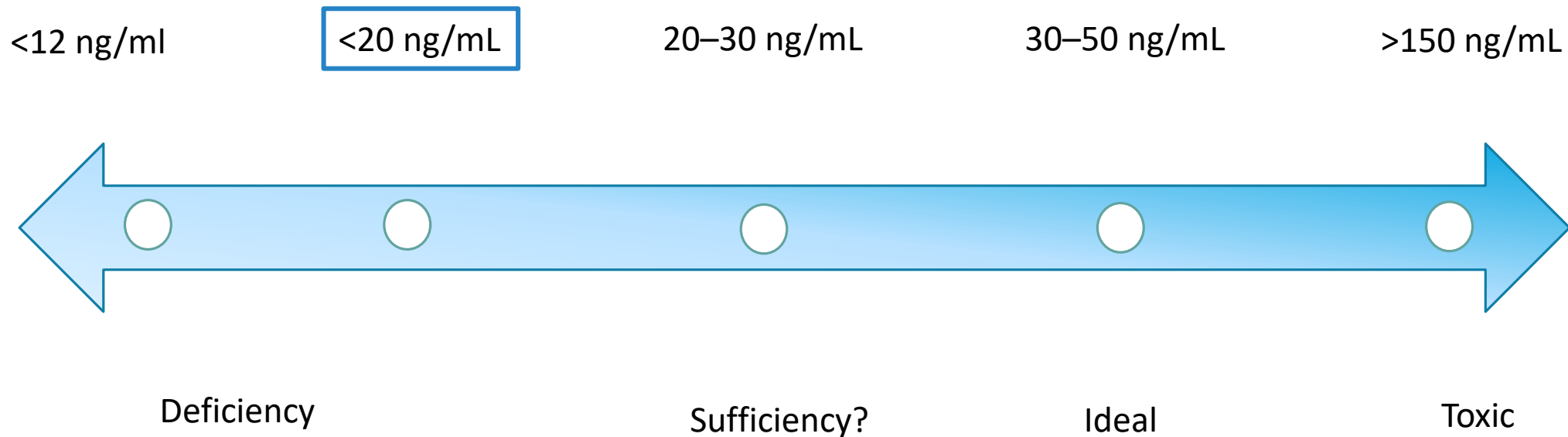
Osteomalacia (Adults)

Epiphyseal plates are closed, no skeletal deformities. Low BMD, **bone pain** and muscle weakness → more frequent falls, higher risk of fracture. Elevated PTH → accelerated bone loss.

Most patients with moderate to mild vitamin D deficiency (15 - 20 ng/mL) are **asymptomatic**.



What is the optimal Vit D level?



IOM a concentration > 20 ng/ml is sufficient for bone health
Endocrinology Society Guidelines recommend at least > 30 ng/ml

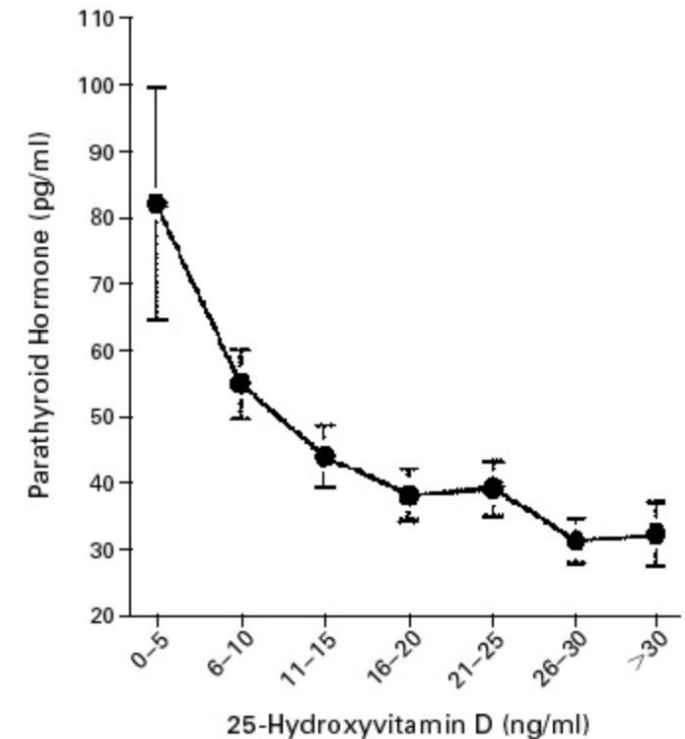
How are the optimal Vit D levels determined?

1. Maximal suppression of PTH

PTH levels increase steeply as Vitamin D levels declined **< 15 ng/ml**. Likely mediated by hypocalcemia

Maximal suppression of PTH occurs with 25(OH)D concentration in the **30 ng/ml**

Other experts support the thesis that suppression of PTH by 25(OH)D follows a continuum across a wide range of vitamin D concentrations and levels above 20 ng/mL



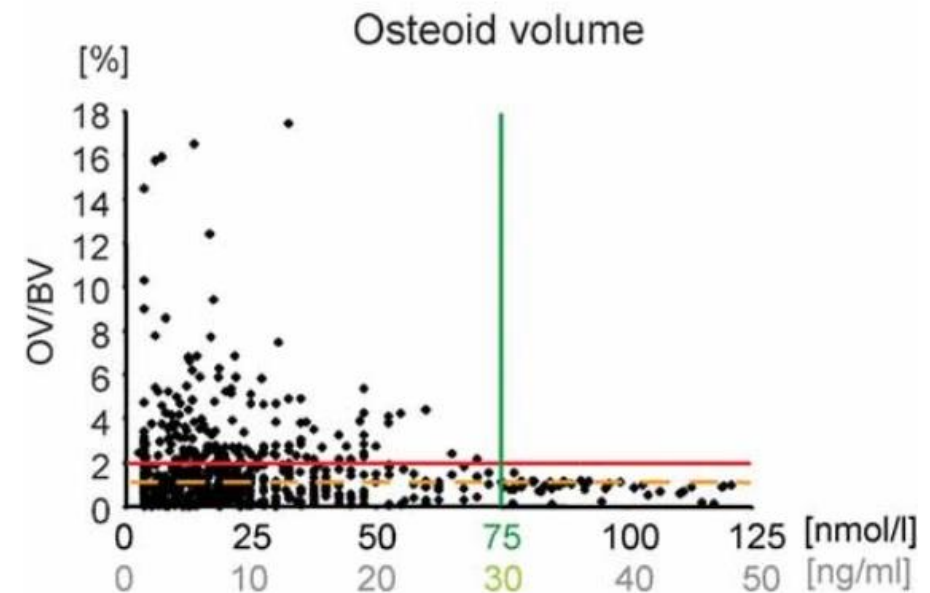
2. Maximal absorption of Ca occurs at >30 ng/ml

How are the optimal Vit D levels determined?

3. Bone health and mineralization

Bone biopsies: 675 iliac crest biopsies from male and female individuals

Increased levels of osteoid (unmineralized bone) with levels **<30 ng/ml** which is a marker of osteomalacia



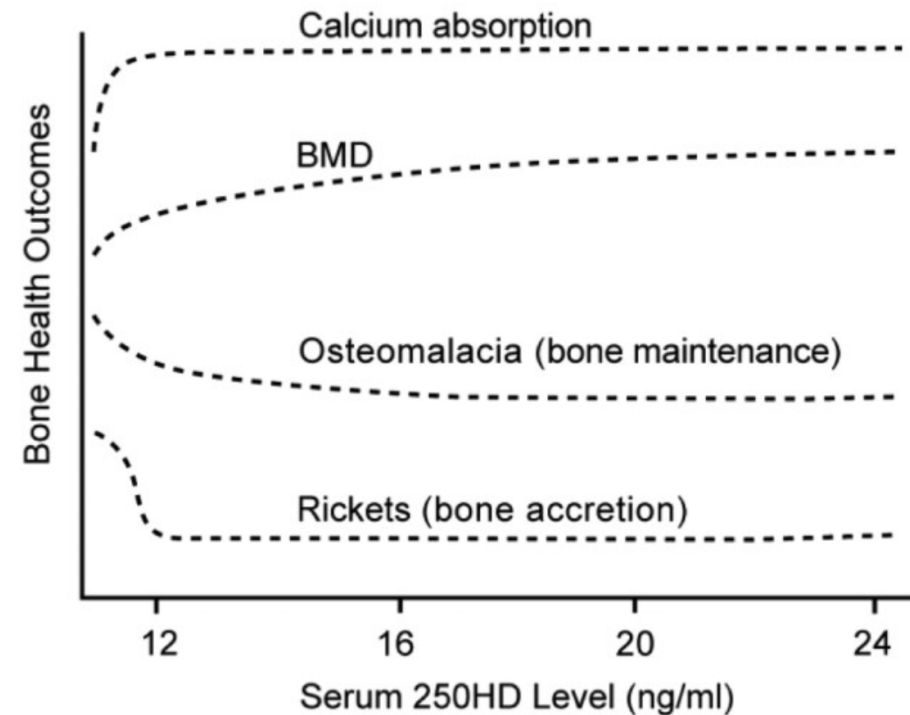
How are the optimal Vit D levels determined?

IOM (Institute of Medicine)

“When the totality of the evidence was considered, there was a notable congruence of data to indicate little or no additional benefit with serum levels above 20 ng/ml and a clear plateau of the effect between 12 and 16 ng/ml.

We did not find that a higher level of serum 25OHD, i.e. 30 ng/ml, would be beneficial for bone health”

What are the Skeletal Health Indicators for Vitamin D?



Lack of standardized testing

There are substantial differences between results in different laboratories with no international standard currently in place.

The two most common ones involve antibodies (immunoassays) or chromatography

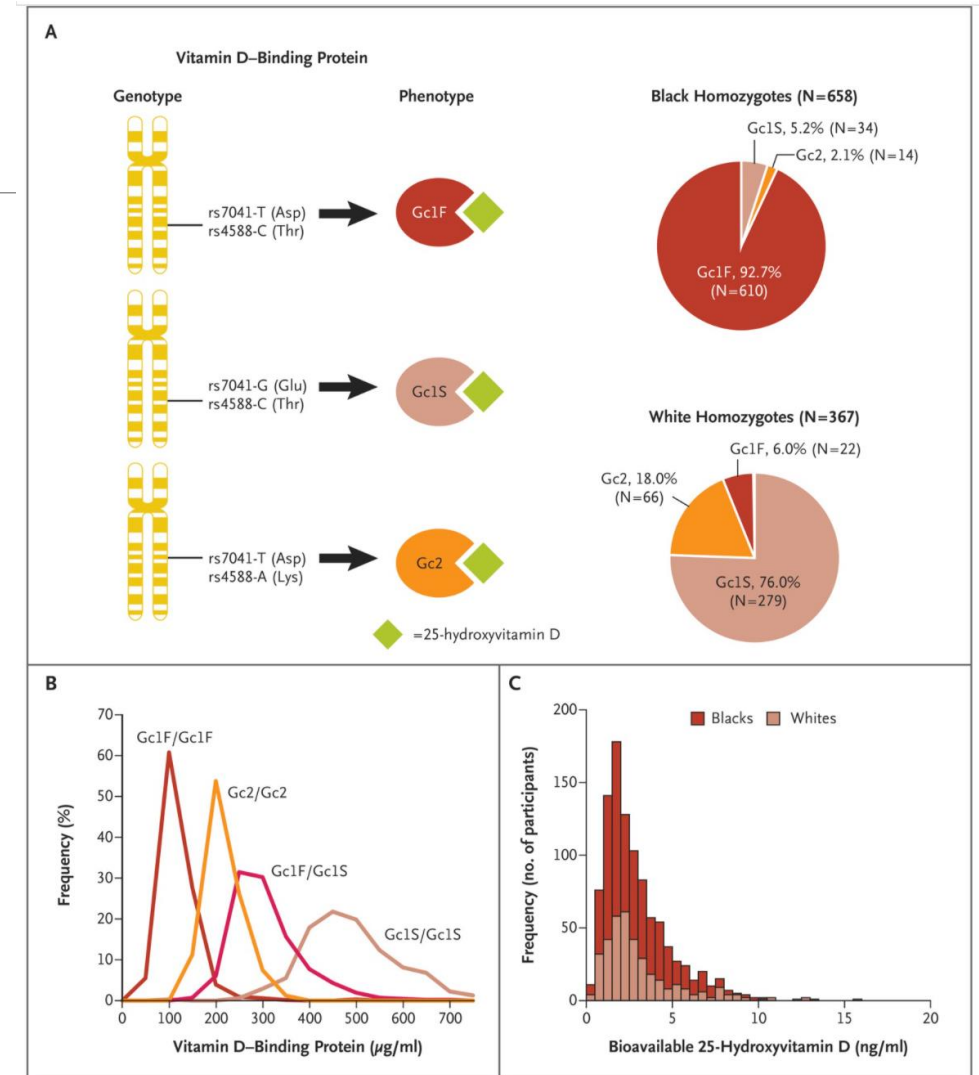
The LC-MS (liquid chromatography-tandem mass spectrometry) is considered the most accurate method and is currently is the gold standard

Vitamin D assays can vary by as much as 10–20 % in the same person



Racial differences

- Levels of total 25(OH) D are consistently lower in black Americans than in white Americans
- Blacks are frequently classified as being vitamin D–deficient.
- Studies show that blacks have lower levels of VDBP that results in levels of **bioavailable 25-hydroxyvitamin D** that are similar to those in whites
- Low levels of vitamin D–binding protein in blacks may provide protection against the manifestations of vitamin D deficiency despite low levels of total 25-hydroxyvitamin D
- It is still not clear if these lower levels have significant health consequences.
- **Blacks have lower rates of bone fracture and osteoporosis than do Whites**



Changes in Vitamin D levels within the individual

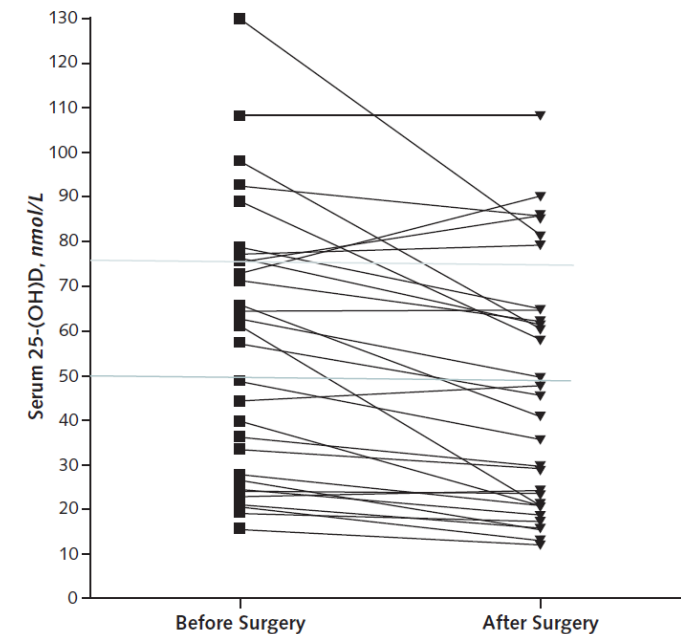
Vitamin D levels decrease during SIRS

- ▶ 25(OH)D is an unreliable marker of vitamin D status during an inflammatory state
- ▶ Hypovitaminosis D may be the consequence rather than cause of chronic inflammatory disease

Negative acute phase reactant?

Vitamin D levels vary widely depending on ethnic background, age, geographic location of the population, and the sampling season.

Figure 3. Changes in 25-(OH)D before and after elective knee surgery.



How much Vitamin D daily to we need?

The Institute of Medicine (IOM) the Recommended Dietary Allowance (RDA)

- *400 IU for children < 12 months*
- *600 IU for children 1- 18 and for adults through age 70*
- *600 IU for pregnancy and lactation*
- *800 IU – 1000IU daily > 70 years old*

* Values assume no endogenous synthesis occurs and the person's source of vitamin D comes entirely from their diet



5–30 minutes of sun exposure, particularly between 10 a.m. and 4 p.m., either daily or at least twice a week to the face, arms, hands, and legs without sunscreen – sufficient Vit D



100 IU/8 oz vitamin D3
Formula



600 IU/3.5 oz vitamin
D3



100 IU/3.5 oz vitamin D2
1,600 IU/3.5 oz vitamin D2
(sun dried)

Vitamin D recommendations in children

- AAP:

- recommends keeping < 6m old out of direct sunlight

- Exclusively and partially breastfed babies **should receive 400 IU of vitamin D** each day continuing up until receiving at least 1 liter or 1 quart of Vit D fortified milk or formula a day

- NHANES 2009–2016 data found that only **20.5%** of breastfed infants met these recommendations.

- Infants in families of lower socioeconomic status were less likely to meet guidelines.

- Children who are obese, on anticonvulsants, steroids or antifungals should receive at least 2 -3 times more Vitamin D



Who should we screen for Vitamin D deficiency?

Endocrine Society and the U.S. Preventive Services Task Force
do not recommend universal screening for vitamin D deficiency among the general population or asymptomatic individuals

TABLE 2. Indications for 25(OH)D measurement (candidates for screening)

| | |
|--------------------------------|---|
| Rickets | |
| Osteomalacia | |
| Osteoporosis | African-American and Hispanic children and adults |
| Chronic kidney disease | Pregnant and lactating women |
| Hepatic failure | Older adults with history of falls |
| Malabsorption syndromes | Older adults with history of nontraumatic fractures |
| Cystic fibrosis | Obese children and adults (BMI > 30 kg/m ²) |
| Inflammatory bowel disease | Granuloma-forming disorders |
| Crohn's disease | Sarcoidosis |
| Bariatric surgery | Tuberculosis |
| Radiation enteritis | Histoplasmosis |
| Hyperparathyroidism | Coccidiomycosis |
| Medications | Berylliosis |
| Antiseizure medications | Some lymphomas |
| Glucocorticoids | |
| AIDS medications | |
| Antifungals, e.g. ketoconazole | |
| Cholestyramine | |

What does Medicare cover?

- **Routine screening is not covered.** Documentation must justify the serum 25-OH Vitamin D testing
- Between 20 and 50 ng/dl, no repeat testing indicated. If <20 or > 60 ng/dl, testing can be reimbursed until reaching normal range

- CKD stage 3 > or greater
- Cirrhosis
- Hypocalcemia, hypercalcemia, hypercalciuria
- Hypervitaminosis D
- Parathyroid disorders
- Malabsorption states
- Obstructive jaundice
- Osteomalacia/ Rickets
- Osteoporosis if T score on DEXA scan <-2.5 or

History of fragility fractures or FRAX > 3% for hip or 20% for other major fracture or FRAX > 3% (any fracture) with T-score <-1.5 or Initiating bisphosphonate therapy

- Osteosclerosis
- Vitamin D deficiency on replacement therapy related to a condition listed above

Vitamin D deficient – now what?

| Vitamin D Levels | Next steps |
|------------------------------|---|
| 12 – 20 ng/ml | No additional evaluation |
| < 12 – risk for Osteomalacia | Ca, Phos, PTH, Alk Phos, BMP. Testing for celiac disease |

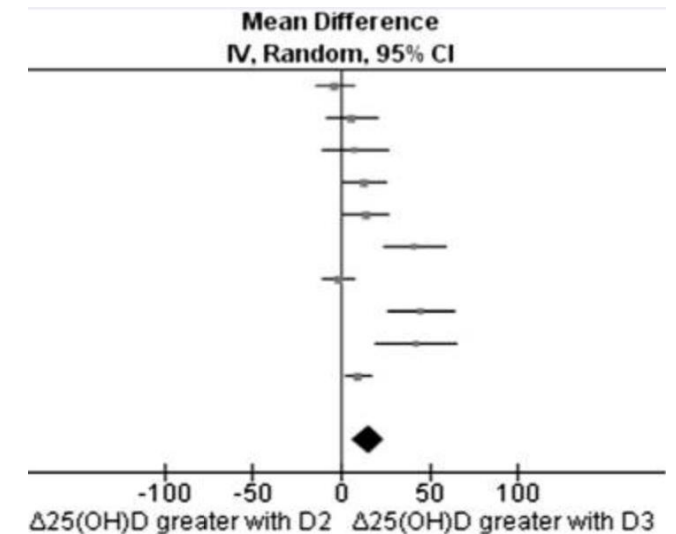
DEXA scan?

- Not routinely if vitamin D deficiency is only risk factor
- If Vitamin D levels were obtained in the setting of osteoporosis. If severely low Vit D and high PTH, osteoporosis treatment should be reevaluated after supplementation.
- There can be a marked increase in BMD after treatment of osteomalacia. Similar with gluten free diet in celiac disease.



Vitamin D2 or D3?

- Both forms are well absorbed in the small intestine
- D2 is made from yeast (might be preferred for vegetarian/vegan patients)
- Vitamin D₃ increases serum 25(OH)D levels to a greater extent and maintains these higher levels longer than vitamin D₂. These differences were mostly seen with weekly/monthly dosing but not daily
- The Endocrine Society recommends using either Vitamin D2 or D3 for supplementation



How much?

Daily, weekly, monthly, yearly or single dose vitamin D dosing regimens can be used.
Importance to keep maintenance dose

| Age | Dose | Maintenance |
|------------------------|--|------------------|
| 1- 18 y | 2000 IU day x 6 weeks or 50000 IU week x 6 – 8 weeks | 600 IU – 1000 IU |
| Adults | 6000 IU day x 8 weeks or 50000 IU week x 12 weeks | 1500 – 2000 IU |
| Obese or malabsorption | 6000 – 10,000 day x 8 weeks | 3000 – 6000 IU |

A review of multiple loading algorithms suggested that a minimum total dose of 600,000 IU best predicted an end of-treatment 25(OH)D level greater than 30 ng/mL

Monitoring of response

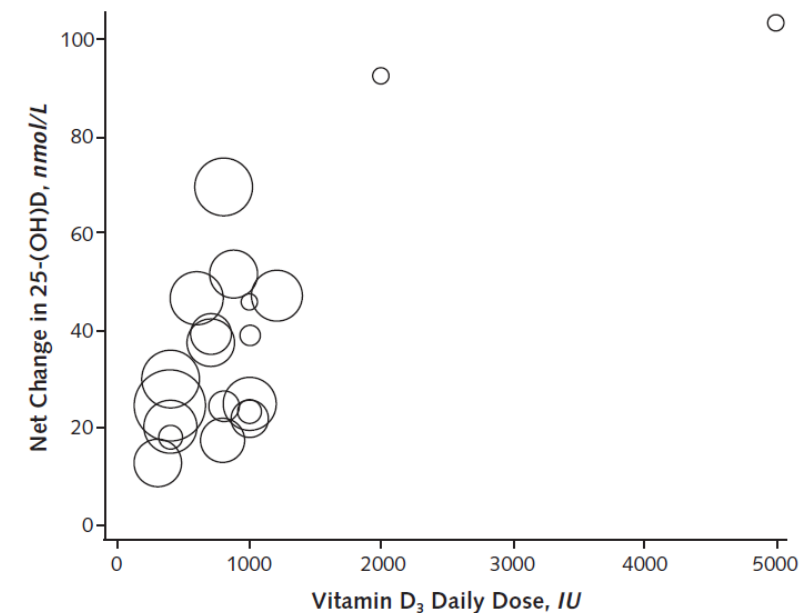
The response of levels is highly variable per patient and in a none linear way. Factors that affect this: baseline Vit D levels and BMI

Repeat levels in 3 -4 months to evaluate response

Should not be done < 8 weeks because this is the time to reach steady state

Some experts recommend testing for celiac disease if there has not been an adequate response to Vitamin D supplementation

Figure 2. Effect of vitamin D treatment on 25-(OH)D levels for a period greater than 3 months.



Is too much Vitamin D harmful ?

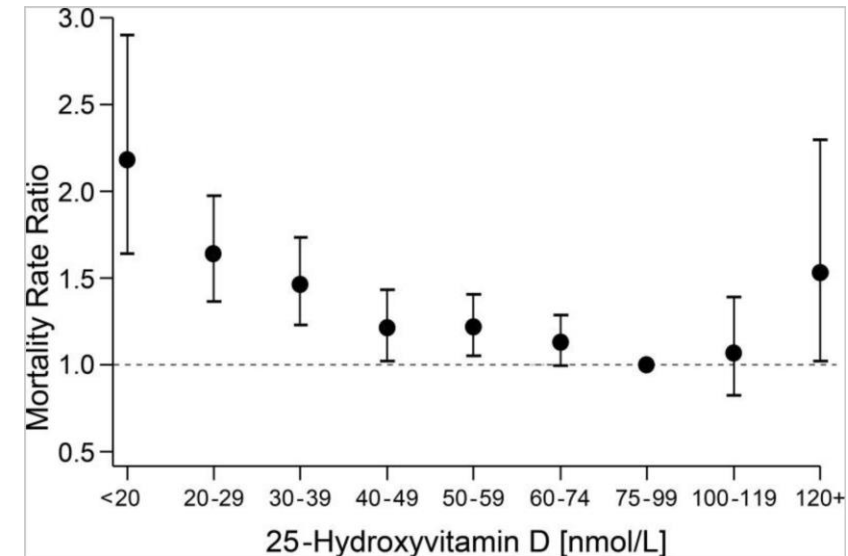
- In general, treatment with vitamin D is not associated with serious harms
- Because Vitamin D is not readily excreted and stored in fat, can build up over time
- Hypervitaminosis D increases absorption of calcium → hypercalcemia, hyperphosphatemia, suppressed parathyroid hormone, and hypercalciuria.
- Symptoms: polyuria, polydipsia, kidney stones, anorexia, confusion, muscle weakness
- Usually levels > 150 - 200 ng/ml
- A 6-yr study of men and women aged 18 – 84 yr who received 3000 IU/d of vitamin D2 reported no change in serum calcium levels or increased risk of kidney stones



Is too much Vitamin D harmful ?



- Too much sun exposure:
 - inactivates vitamin D metabolites preventing toxicity.
 - stimulates melanin production which prevents additional vitamin D production.
- Very high doses of Vit D have been associated with increased risk of falls in the elderly (>500,000IU/year)
- IOM recommends avoiding serum levels **> 50 – 60 ng/ml**, associated with increases in rates of all-cause mortality (“J” curve) risk of cancer at some sites (e.g., pancreas), risk of cardiovascular events, and number of falls and fractures among older adults.



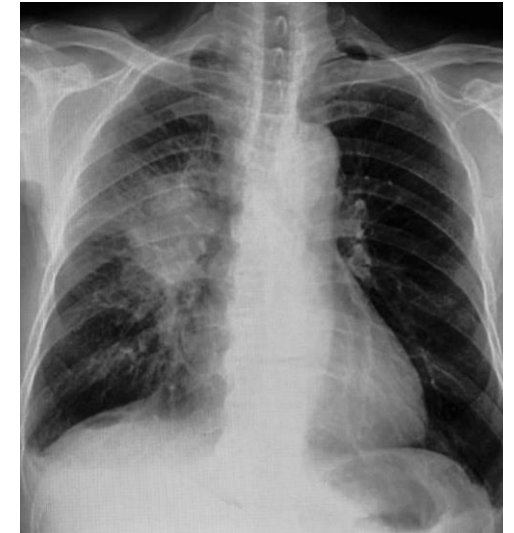
Any contraindications?

- Granulomatous disease (tuberculosis)
- Sarcoidosis
- Chronic fungal infections
- Lymphomas

High 1,25(OH)₂D → more risk of hypercalcemia.

Thiazide diuretics

Decrease urinary calcium excretion. The combination of these diuretics with vitamin D supplements (which increase intestinal calcium absorption) might lead to hypercalcemia, especially among older adults and individuals with compromised renal function or hyperparathyroidism. **Supplements up to 4000 IU appear to be safe and not cause significant hypercalcemia.**



Does Vitamin D supplementation....?

Reviewing the latest evidence



Prevent falls in the elderly?

In 2012 the USPFTS recommended Vit D supplementation to prevent falls

2018 updated guidelines recommend against supplementation in patients not known to have Vit D deficiency

2020 VITamin D and OmegA-3 Trial (VITAL) : 26,000 community-dwelling middle-aged or older adults received 2000 IU of vitamin D₃ or placebo and had a follow up of 5 years. At baseline, mean 25[OH]D level was 31 ng/mL No protective effect of vitamin D supplementation was evident in any subgroup — including thos with baseline low Vitamin D



The current evidence shows no benefit that Vitamin D supplementation prevents falls.



Vitamin D/Ca and prevention of fractures

Many clinical trials with both vitamin D and calcium result in small increases in BMD in elderly

Systematic reviews: NEJM 2012 High-dose vitamin D (≥ 800 IU daily) was somewhat favorable in the prevention of hip fracture and any nonvertebral fracture in persons 65 years of age or older.

USPSTF 2018: 11 randomized clinical trials of vitamin D (400IU)w calcium supplementation in a total of 51,419 healthy, community-dwelling adults aged 50 years and older who did not have osteoporosis, vitamin D deficiency, or prior fractures. Recommends against supplementation of 400IU in this population, unclear benefit of higher doses.



Apparent reduction in fractures associated with vitamin D when given at moderate doses (≥ 800 IU/day) together with calcium (500 mg/day)

Prevent primary CV events or cancer?

Randomized Clinical Trials → treatment with vitamin D does not prevent CV disease.

Women's Health Initiative: Calcium & Vit D supplementation had no effect on incident coronary or cerebrovascular events. Perhaps this was due to a low Vit D dose of only 400 IU daily. Other studies in 2017 (JAMA) did not find lower incidence of cancer with 2000IU D3 in postmenopausal women

ViDA Study: (New Zealand) monthly high-dose Vit D (100,000 IU of D3) did not prevent CV disease, including 25% of patients who had level < 20 ng/mL. Atypical supplementation regimen.

Vital Trial: neither n-3 fatty acid (1g/day) nor Vit D3 (2000 IU/day) were effective for primary prevention of CV or cancer events among healthy adults 5 years of follow-up. This was among the largest of the Vit D supplementation trials and included substantial black participants.



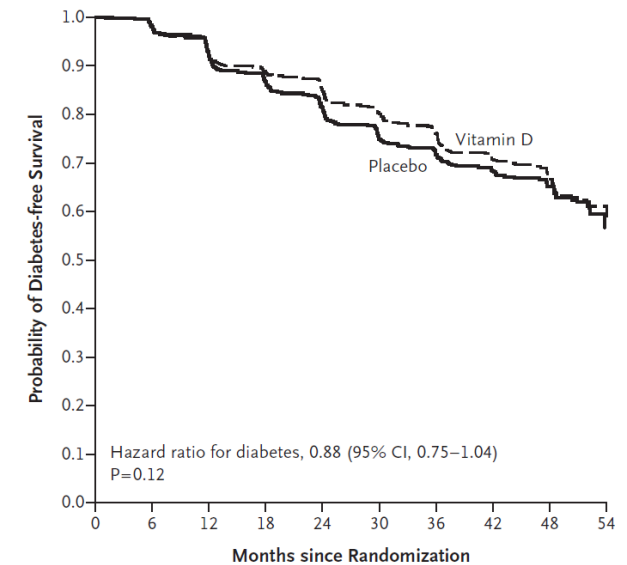
Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo.

Vitamin D Supplementation and Prevention of Type 2 Diabetes

Both impaired pancreatic beta-cell function and insulin resistance have been reported with low blood 25-hydroxyvitamin D levels. Observational studies support an association between a low Vit D and the risk of diabetes

D2d Trial multicenter, randomized, placebo-controlled trial involving 2400 persons at high risk for type 2 diabetes, taking 4000 IU of vitamin D₃ or placebo.

80% of patients had adequate levels of vitamin D may have limited the ability of the trial to detect a significant effect.



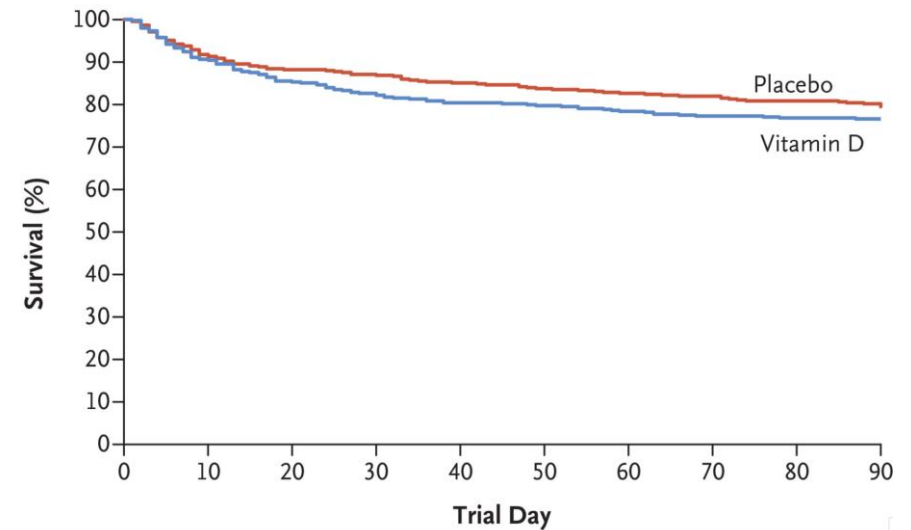
| No. at Risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
|-------------|------|------|------|------|-----|-----|-----|-----|-----|----|
| Vitamin D | 1211 | 1171 | 1089 | 1001 | 812 | 625 | 466 | 283 | 141 | 21 |
| Placebo | 1212 | 1171 | 1091 | 975 | 779 | 577 | 419 | 258 | 121 | 13 |



Vitamin D₃ supplementation did not result in a significantly lower risk of diabetes than placebo after a median follow-up of 2.5 years.

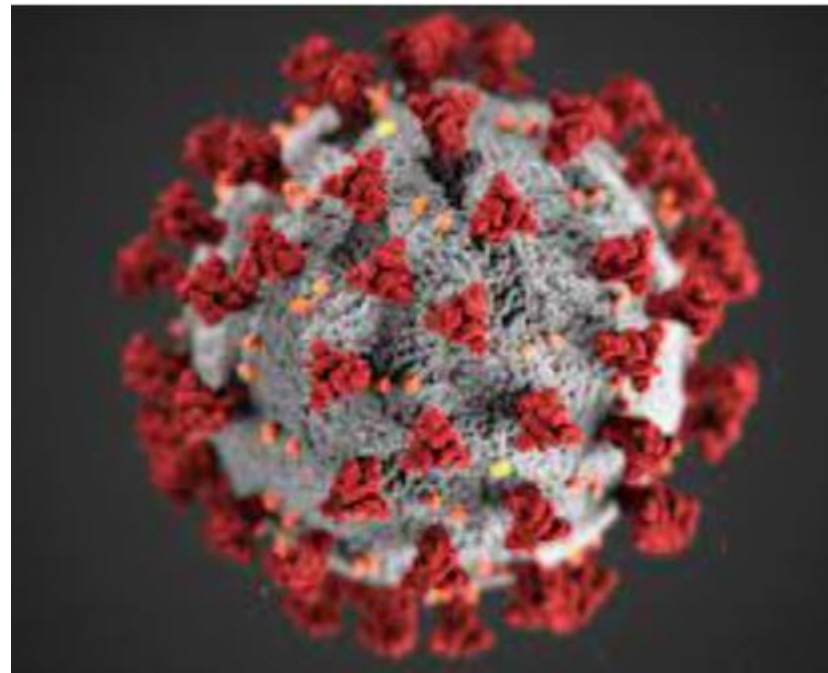
Early High-Dose Vitamin D3 for Critically Ill, Vitamin D–Deficient Patients

VITdAL-ICU: multicenter, double-blind, placebo-controlled, A total of 1360 patients were found to be vitamin D–deficient and underwent randomization vitamin D₃ regimen (a single enteral dose of 540,000 IU), the threshold for vitamin D deficiency <20 ng/ml, and a focus on critically ill patients.



Early administration of high-dose enteral vitamin D₃ did not provide an advantage over placebo with respect to 90-day mortality or other, nonfatal outcomes among critically ill, vitamin D–deficient patients

What about COVID-19 and Vitamin D?



Clinical Research Article

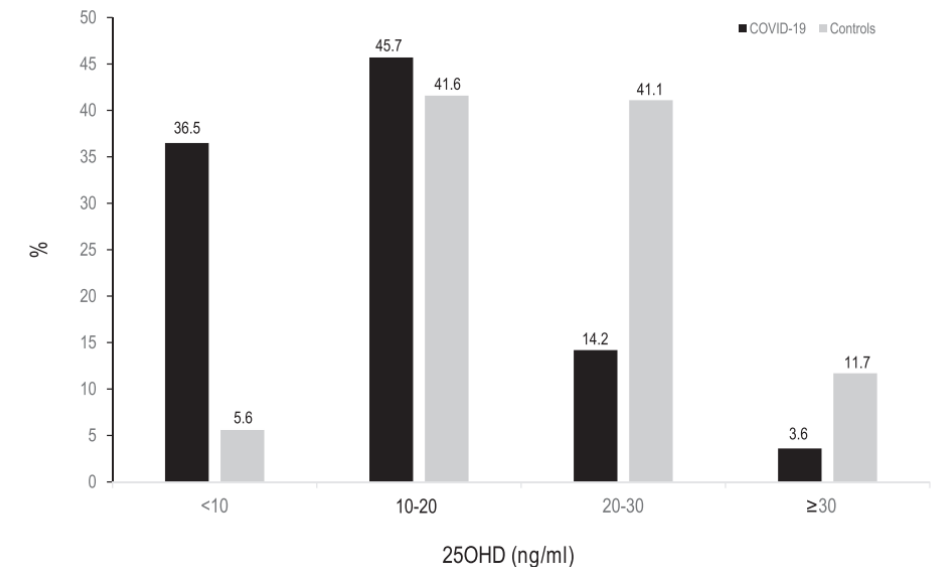
Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection

José L. Hernández,^{1,10} Daniel Nan,^{1,10} Marta Fernandez-Ayala,¹

Retrospective case–control study of 216 COVID-19 patients and 197 population-based controls in Spain.

Key findings:

Vitamin D deficiency was found in **82.2% of COVID 19 cases**
Did not find any relationship between vitamin D concentrations or vitamin deficiency and the severity of the disease

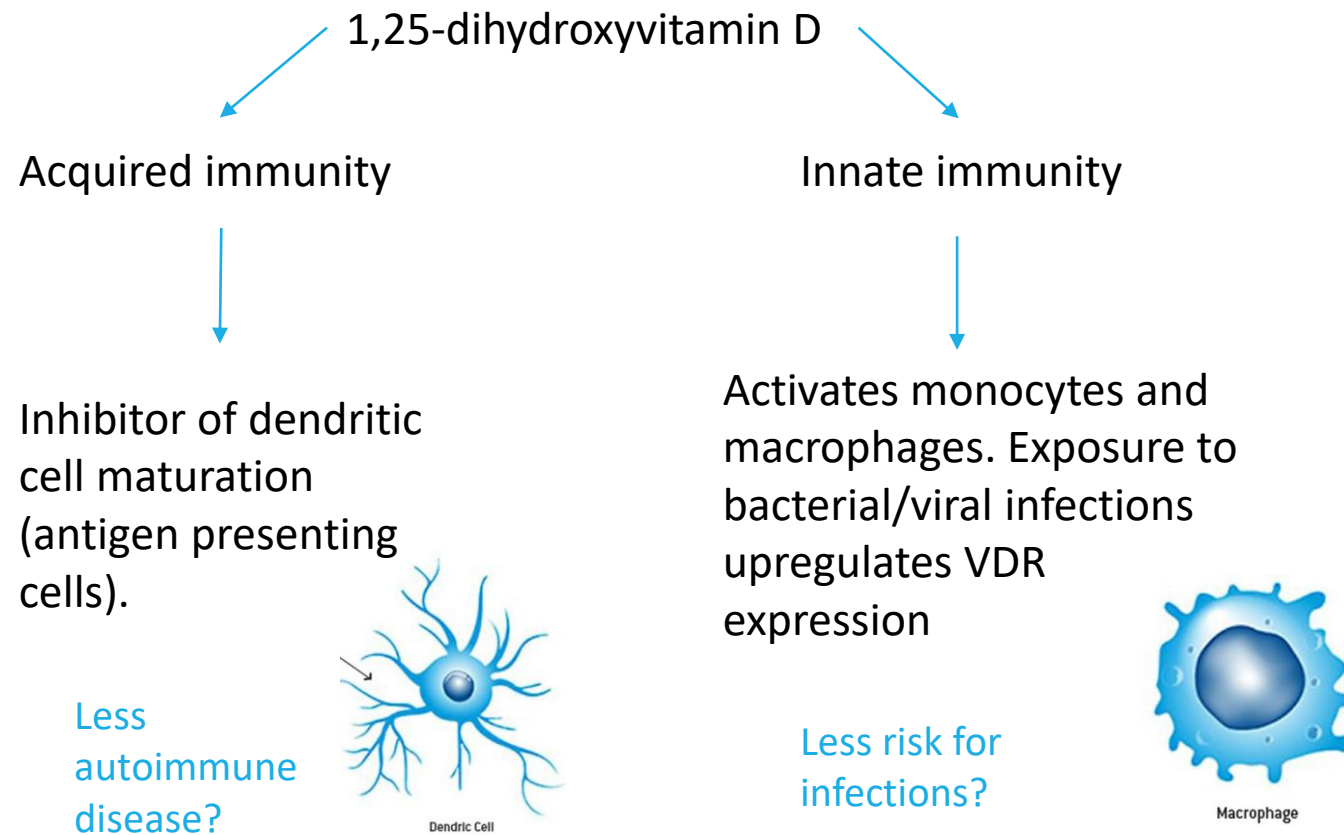


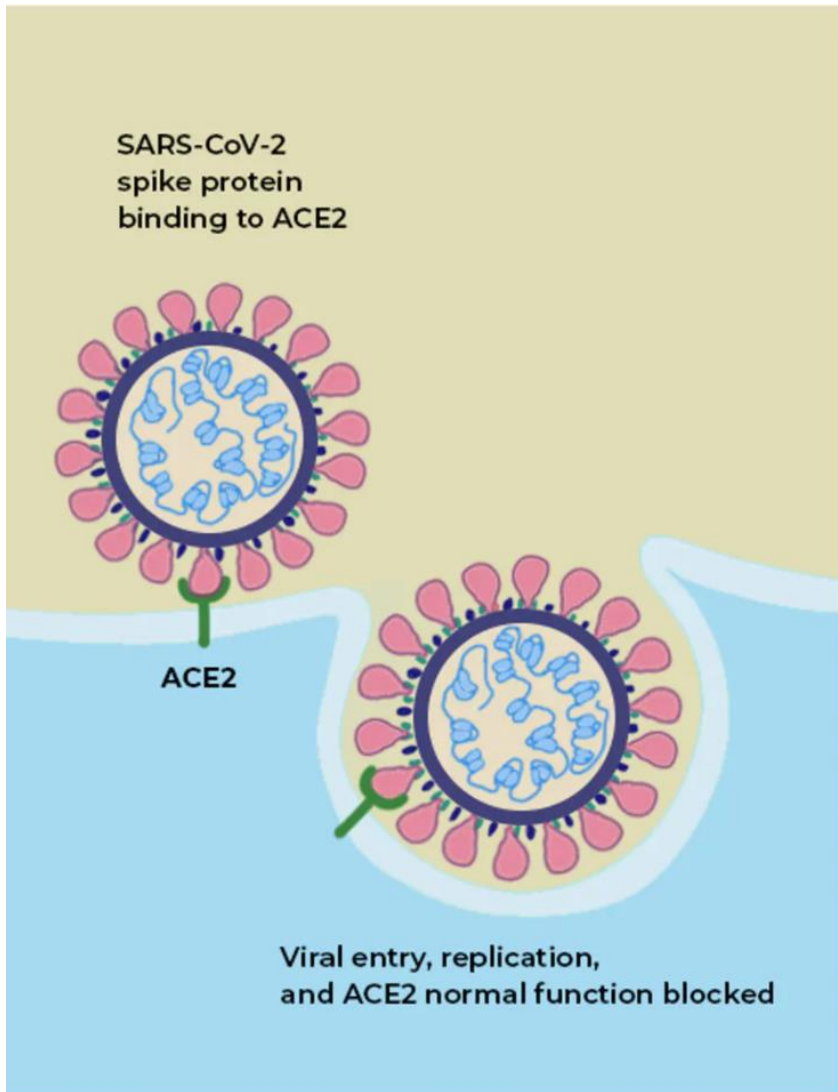


Vitamin D and COVID-19

- Population at risk: older adults and nursing home residents, and Black, Asian, and minority ethnic populations, are more likely to be Vitamin D deficient and have poor COVID-19 outcomes.
- Increased time spent indoors due to strict lockdowns
- Many health institutions recommended to take vitamin D supplements to maintain bone and muscle health during lockdowns
- European countries set initiatives to allow vulnerable people to opt in to receive a free 4-month supply of daily vitamin D supplements

Vitamin D and immunity





Vitamin D and COVID-19

- Vitamin D has effect on the RAS system, specifically the expression of ACE 2 receptor
- ACE 2 serves as an entry point for COVID-19 virus, reducing its expression and causing lung injury and pneumonia
- Vitamin D could prevent the downregulation of ACE 2 in patients infected with SARS-CoV-2 thus, avoiding persistent lung injury

Effect of a Single High Dose of Vitamin D₃ on Hospital Length of Stay in Patients With Moderate to Severe COVID-19

Largest published randomized, double-blind, placebo-controlled trial of vitamin D₃ administration among hospitalized patients with COVID-19 to date. In Brazil

240 hospitalized patients with moderate to severe COVID-19, a single dose of 200 000 IU of vitamin D₃, compared with placebo, did not significantly reduce hospital length of stay. Only (48.3%) had vitamin D deficiency (25[OH]D <20 ng/mL)



The study does not support the use of a high dose of vitamin D₃ for treatment of moderate to severe COVID-19 in hospitalized patients.

Why are we disappointed by Vitamin D studies?

- Most RCTs include participants regardless of their vitamin D status or higher concentrations of Vit D.
- May miss significant vitamin D effects in 'sensitive' populations such as vitamin D-deficient individuals.
- Lack of consensus of what constitutes Vitamin D deficiency
- Lack of standardization for testing methods and international recognized reference range
- Under powering: needing larger number of participants to measure differences.
- Difference in dosing, difference in effect for different populations (obese)
- Variability in assay – or effect of supplementation? Especially with lower doses.
- Correlation does not mean causation

Joint guidance on vitamin D in the era of COVID-19



- For those unable to spend at least 15-30 minutes with direct sun exposure each day → recommends supplementation. Most adults can safely take 400-1000 IU daily to keep vitamin D levels within the optimal range
- Low Vitamin D and higher rates of COVID-19 infection are likely related to ethnicity, age, and general health rather than a causal relationship
- **The current data does not provide any evidence that vitamin D supplementation will help prevent or treat COVID-19 infection.**
- Vitamin D is very safe when taken at reasonable dosages and is important for musculoskeletal health.

Take home points

1. Vitamin D is important for bone health. Probably has extra skeletal effects, but studies have failed to consistently show benefits.
2. There is no consensus on the optimal levels and there is high variability between individuals and populations
3. Screening in healthy populations have not shown benefit in health outcomes
4. Remember to start all breastfeeding and partially breastfeeding infants on 400IU/daily
5. Could consider recommending supplementation especially during winter months in northern latitudes, darker skin individuals, and or spending much time inside
6. Treatment with Vitamin D is generally safe with minimal side effects and low risk for toxicity



CHILE

Thank you!



The NEW ENGLAND
JOURNAL of MEDICINE



Case 39-2020: A 29-Month-Old Boy with Seizure and Hypocalcemia

Yamini V. Virkud, M.D., M.P.H., Neil D. Fernandes, M.D., Ruth Lim, M.D.,
Deborah M. Mitchell, M.D., and William T. Rothwell, M.D., Ph.D.