

Handouts for Participants:

**Vitamin D Deficiency:
How it Relates to Patients with Developmental
Disabilities and Ways to Correct it**

“Vitamin D Symposium”

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AADMD– Vitamin D Symposium; 06/18/2014

Vitamin D Deficiency: How it Relates to Patients with Developmental Disabilities and Ways to Correct it

Sunil Wimalawansa, MD, PhD, MBA

Vitamin D: An Essential Hormone

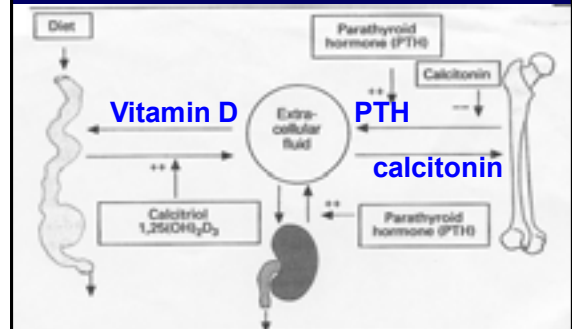
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Outline

- Vitamin D basics, functions, and Prevalence of vitamin D deficiency
- Vitamin D₂ vs. D₃ – what to prescribe?
- Definitions and ways to treat Vit. D deficiency
- Consequences of low vitamin D status
- Health Benefits and Non-Skeletal Effects of Vitamin D in Developmental Disable

Major Physiological Regulatory Mechanisms in Calcium Metabolism

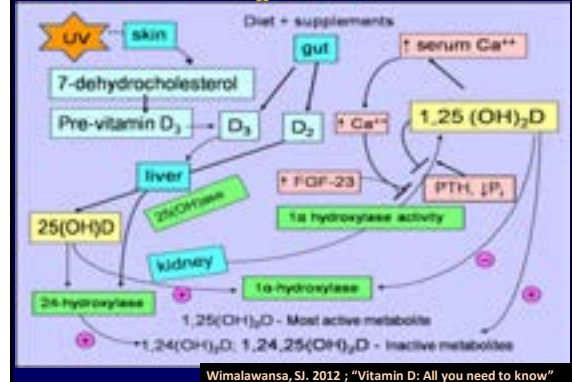


Active Vitamin D is a Hormone

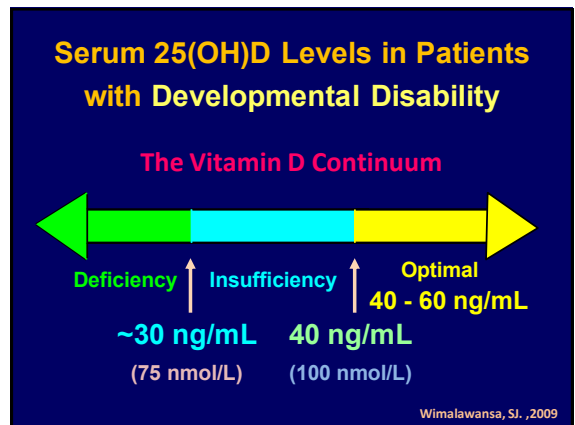
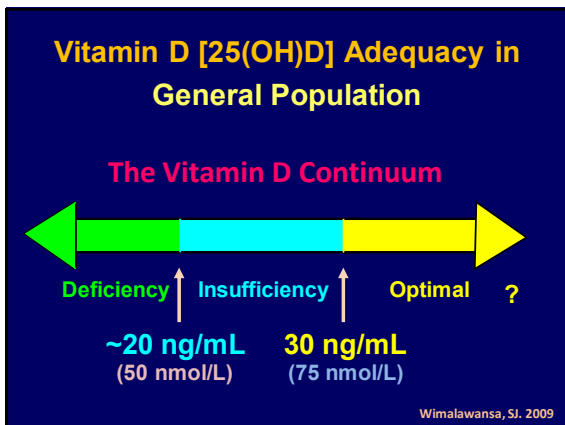
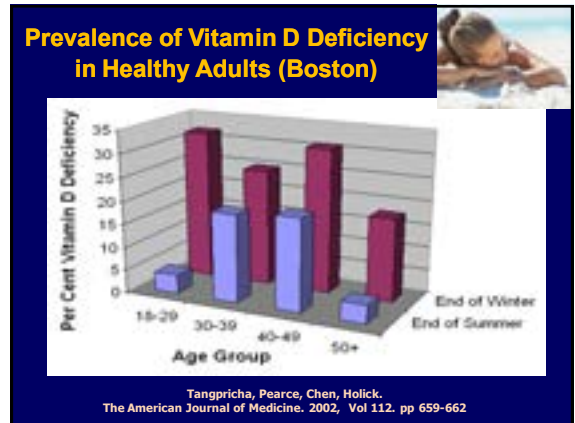
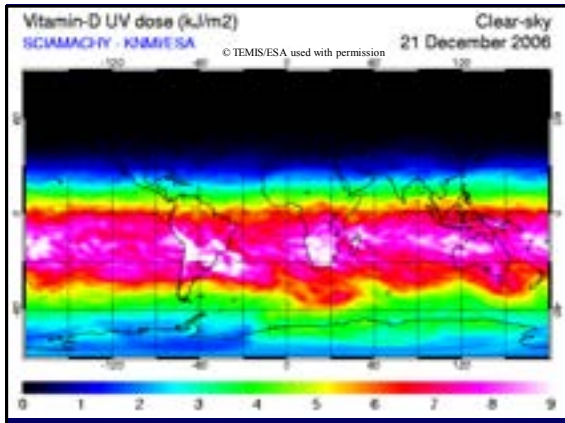
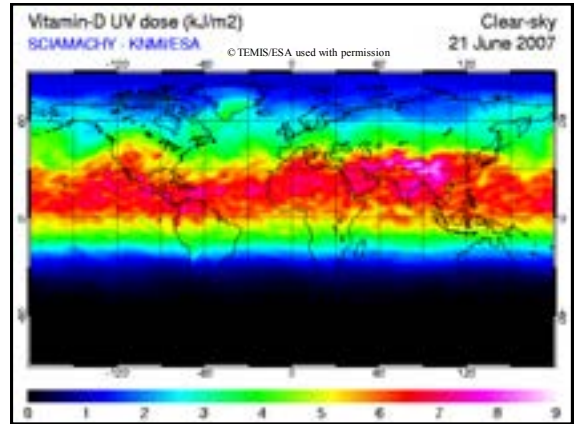
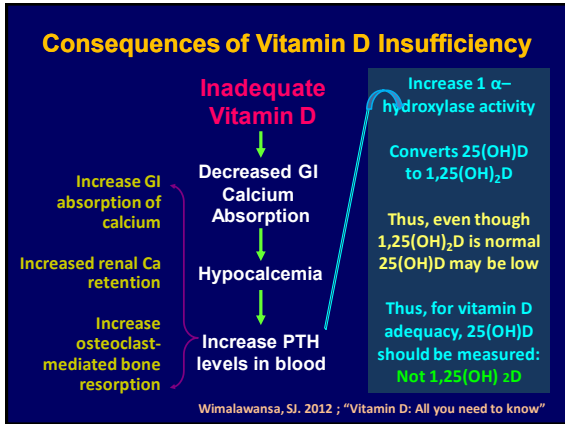
- Vitamin D is a major steroid hormone among others involved in homeostatic regulation of mineral ions
- Vitamin D and its metabolites are hormones and hormone precursors rather than vitamins, and (supposed to be) usually synthesized endogenously

Wimalawansa, SJ. 2012 ; "Vitamin D: All you need to know"

Mechanisms and generation of Vitamin D



Wimalawansa, SJ. 2012 ; "Vitamin D: All you need to know"



Developmentally Disabled Patients

- Over 70% of are on medications that increase catabolism of 25(OH)D (CYP 3A4)
- Little or no exposure to sunlight
- Many have malabsorption issues
- Diet provide very little vitamin D
- To control many comorbidities requires higher serum vitamin D levels (>40 ng/mL)
- Standard supplementation of 400 to 600 IU per day is grossly inadequate

Wimalawansa, SJ. 2012 ; "Vitamin D: All you need to know"

Vitamin D Status: Terminology

	General Public ng/mL	For DD population ng/mL
• Deficiency	< 15	< 29
• Insufficiency	15 – 29	30 – 39
• Normal (lab) range	30 – 70	30 – 100
• Preferred range	30 – 50	40 – 60
• Intoxication	> 150	> 150

Wimalawansa, SJ. 2009

Who is Vitamin D Deficient? Everyone



Who Should be Screened for Vit. D?

- To check the vit. D "adequacy", one need to measure serum 25(OH)D levels
 - 1,25(OH)₂D is indicated in CKD patients
 - CKD; hypercalcemia; granulomatus disease
- Screening population and individuals who are not at risk is not recommended
- All high risk individuals should have baseline serum 25(OH)D checked

Wimalawansa, SJ. 2012 ; "Vitamin D: All you need to know"

Recommendation for Vit. D Screening

- Screening for vitamin D deficiency is recommended for those individuals who are at high risk for D deficiency, including:
 - Patients with osteoporosis / fractures
 - Those with malabsorption syndromes
 - Those with dark skin: Africans, Asians, Hispanics
 - Obese persons (BMI >30 kg/m²)
 - Patients with chronic kidney disease

Wimalawansa, SJ. 2012 ; "Vitamin D: All you need to know"

In addition to sequestration of vitamin D in fatty tissues, there are other relationship of excess body fat and decreased 25(OH)D levels



Wimalawansa, SJ. 2012 ; "Vitamin D: All you need to know"

Actions of Vitamin D

- **Musculo-skeletal and Mineral Modulating Actions of Vitamin D**
- **Non-Classical Actions (and non-skeletal targets) of Vitamin D**

Vitamin D Has Local Effects

- Vitamin D receptors present in over 30 tissues
- Essentially all tissues have 25 hydroxylase
- Many tissues (not just kidney) possess 1 α -hydroxylase (CYP27B1)
 - Intestine, muscle, islet cells, monocytes, B & T cells, neurons, chondrocytes, colonic enterocytes, prostate, ovary, endothelial cells.....
- 1, 25(OH)₂D can be produced locally in many tissues
- “The non-classical actions of vitamin D are cell specific and provide a number of potential new clinical applications for 1,25(OH)₂D₃ and its analogs.”

Bikle, J Clin Endo Metab, 94:26-34, 2009

Basic Facts About Vitamin D

- **Breast milk has minimal amounts of vitamin D. Thus, the American Academy of Pediatrics recommends vitamin D supplementation starting at age 2 months for infants fed exclusively with breast milk.**
- **Diseases associated with vitamin D malabsorption include celiac sprue, any short bowel syndromes, cystic fibrosis.**

Wimalawansa, SJ. 2012 ; “Vitamin D: All you need to know”

Basic Facts About Vitamin D

- **A 25(OH)D level of less than 30 ng/mL is considered vitamin D insufficient (< 40 ng/mL for DD patients).**
- **A 25(OH)D level of less than 20 ng/mL is defined as vitamin D deficiency (< 30 ng/mL)**
- **Intestinal calcium absorption is optimized at 25(OH)D levels of more than 32 ng/mL**
- **Parathyroid hormone levels start to rise at 25(OH)D levels less than 30 ng/mL. Thus, it is a marker for vitamin D insufficiency.**

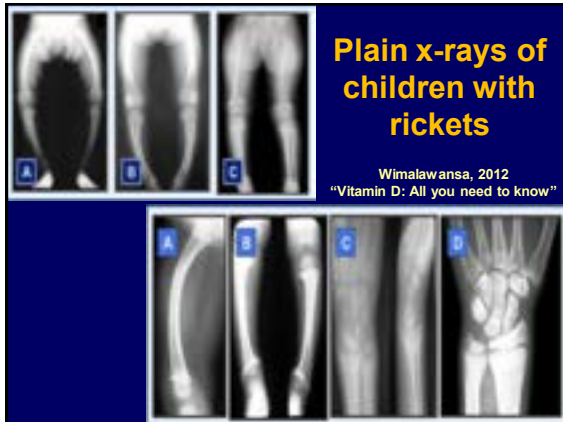
Wimalawansa, SJ. 2012 ; “Vitamin D: All you need to know”

QUIZ 1: Vitamin D insufficiency is more common in which of the following groups?

- **Among the elderly**
- **Among hospitalized patients**
- **African-American and Hispanics**
- **Patients with developmental disabilities**
- **During the winter months**
- **All of the above**

Severer Vitamin D Deficiency

Although vitamin D deficiency is often clinically silent, it can lead to rickets in children and osteomalacia in adults



Examples of High-Risk Individuals

- Rickets and osteomalacia
- Osteoporosis / low BMD / fragility fractures
- All malabsorption syndromes
- Chronic kidney disease
- Obese; Pre- and post-bariatric surgery
- Hyperparathyroidism
- Some ethnic minority groups
- Granulomatous disorders & lymphomas
- Taking certain medications

Wimalawansa, SJ, 2012 ; "Vitamin D: All you need to know"

Medications that Decrease levels of Serum 25(OH)D



- Most anti-seizure medications
- Glucocorticoids
- Most medications use for AIDs
- Anti-fungal (e.g., ketoconazol)
- Cholestyramine, heparin, etc...
- [Any agent increase the activity of hepatic cytochrome] - P450 3A4 (CYP 3A4)

Wimalawansa, SJ, SLJ of Diabetes, Endocrinology & Metabolism; 2: 73-88, 2012

Examples of Granulomatous Diseases That Could Lead to extra-Renal Generation of 1,25(OH)₂D

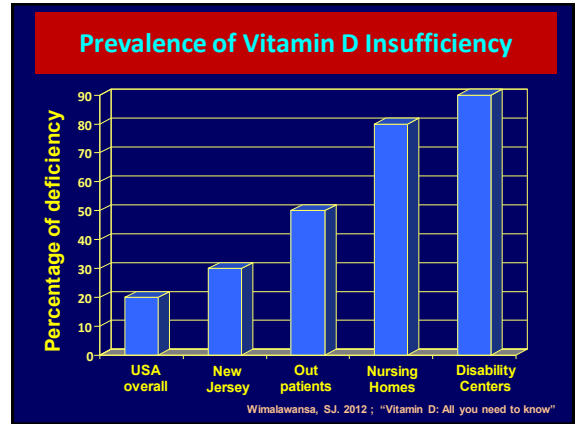
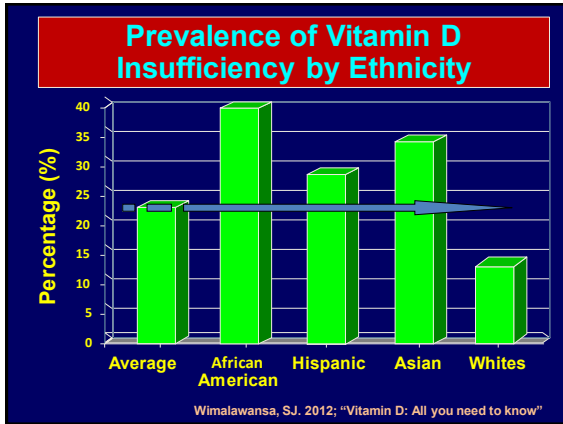
- Sarcoidosis
- Tuberculosis
- Coccidiomycosis
- Histoplasmosis
- Beryliosis

Wimalawansa, SJ, SLJ of Diabetes, Endocrinology & Metabolism; 2: 73-88, 2012

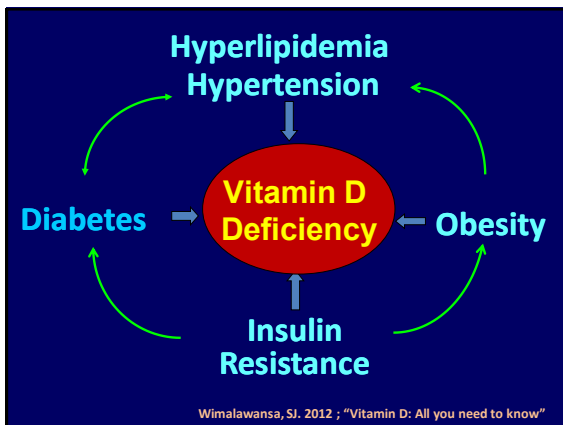
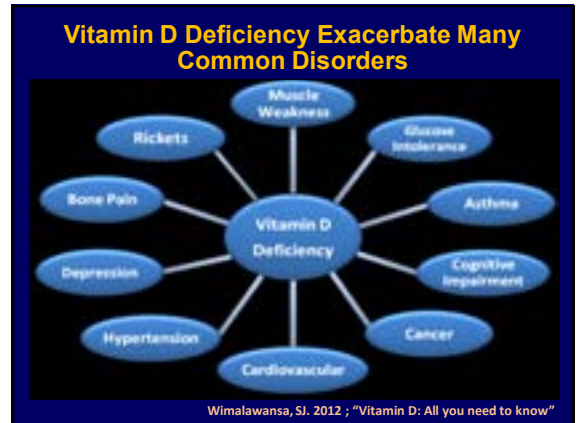
Key Risk Factors for Development of Vitamin D Deficiency

- ↓ exposure to sunlight/winter season
- Garments that prevent skin exposure
- Atmospheric pollution
- In northern or southern latitudes
- Sunscreens with SPF greater than 12
- Elderly, and institutionalized patients
- Cognitively impaired, homebound, non-ambulatory
- Developmental disability centers and nursing homes
- ↓ synthesize vitamin D in the skin:
 - Being African-American or Asian
 - Having darker skin; Older age
 - Avoiding sun exposure
 - Scarred skin or previously burned skin
- Agents interfering vitamin D metabolism
- Pregnancy and childhood:
 - Multiple, short-interval pregnancies
 - Prolonged breastfeeding
- Dietetic habits
- Personal, social, & cultural factors
- Vegetarianism & non-fish diets
- Malabsorption syndromes
- Inflammatory diseases
- Concomitant illnesses: Chronic renal failure; renal tubular diseases
- Hyperparathyroidism; liver diseases
- Obesity or rapid weight loss after diet/bariatric surgery

Wimalawansa, SJ, 2012 ; "Vitamin D: All you need to know"



Vitamin D Deficiency Contributes to Escalation of a Multiple Disorders Affecting Humans



Vitamin D: Prevention of Falls and Fractures

"Low serum 25(OH)D concentrations are associated with a higher risk for hip fracture."

Bishops et al; Cauley, et. al., Ann Int Med; 149:242-250, 2008

Reducing the Risks of Osteomalacia, Osteoporosis, Fracture, Falls, and Cancer are Excellent Reasons for me to Treat My Patients With Vitamin D to bring their Serum 25(OH)D levels above 30 ng/mL

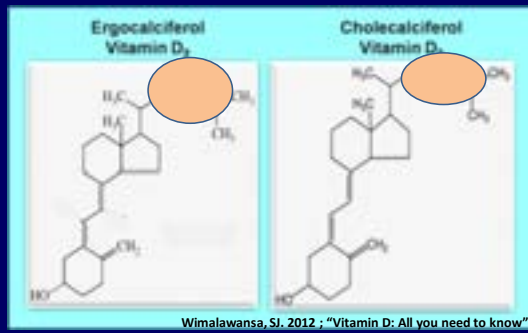
Wimalawansa, SJ, 2008

Potential Beneficial Effects of Vitamin D



Wimalawansa, SJ, 2012 ; "Vitamin D: All you need to know"

Structures of Pro-hormones: Vitamin D₂ and D₃



Wimalawansa, SJ, 2012 ; "Vitamin D: All you need to know"

Vitamin D₂ or D₃ – What to Use?

- D₂ is from plant sources and D₃ is from animal sources
- When given daily or weekly basis, D₂ and D₃ are equipotent in raising serum 25(OH)D levels
- Due to the longer half life, D₃ is recommended for once in two weeks or monthly supplementation

Wimalawansa, SJ, *Annals of New York Acad Sci*, NY, 2012, 1240: E1-12, 2012

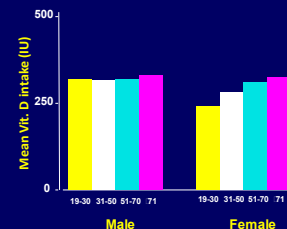
Which Form of D to Take?

- Vitamin D represents D₂ and D₃:
- Ergocalciferol (vitamin D₂):
 - From irradiation of yeast/plant sterol ergosterol
 - Primary commercial product
 - Half-life of 25-OH D₂: 8-10 days
- Cholecalciferol (vitamin D₃):
 - From oily fish and cod liver oil
 - Synthesized in the skin
 - Half-life of 25-OH D₃: 25-30 days

Wimalawansa, SJ, *Annals of New York Acad Sci*, NY, 2012, 1240: E1-12, 2012

Vitamin D is Uncommon in Food Intake Low At All Ages

Food	IU
Cod liver oil, 1 tbs	1360
Salmon, 3.5 oz	360
Milk, 1 cup	100
Liver, 3.5 oz	30
Egg, one whole	25



NHANES III data; mean vitamin D intake from food plus supplements

Moore, et. al., *Am Diet Assoc*, 104:980-983, 2004

What Foods Are Fortified? Current Status, USA

(Food Label and Package Survey)

- Fortified milk products (8 oz) - 100 IU
- Fortified orange juice (8 oz) - 100 IU
- Fortified cereal (1 serving) - 40-80 IU
- Canned salmon with bones (100g)-624 IU
- Yogurts (~25%)
- Cheeses (100 g) – 35 to 60 IU
- Sun-exposed mushroom (100 g) – 50-100 IU
- Most multivitamins (1 tab) - 400 to 1,000 IU
- [Mostly D₂]

Wimalawansa, 2012: Yetley, EA, Am J Clin Nutr; 88(suppl):558S-564S, 2008

Vitamin D Assays: Which one is Reliable?

Assays available for vitamin D measurements:

- 25(OH)D: is the standard clinical measure
- Immunoassays: RIA & ELISA measures total 25(OH)D, including 25(OH)D₂ and 25(OH)D₃
- HPLC and LC: MS:MS – Measure D₂ and D₃ separately
- 1,25 (OH)₂ D is the active form, but is not a good measure of vitamin D status (labile, & short half-life). Hence it should not be measured

Holick MF. NEJM. 2007; 357: 266-81

Correction of Vitamin D Deficiency

For those who are with serum vitamin D levels < 20 ng/ml):

- 50,000 IU, once a week, for 12–16 weeks
- 50,000 IU, twice a week, for 6–10 weeks
- 200,000 IU loading dose, and 50,000 IU Once in 2 weeks, for 12 weeks
- Followed up with 2,000 IU per day maintenance dose

Wimalawansa, S.J., Current Osteoporosis Research, 10:4-15, 2012

Basic Principles in Rx Vit. Deficiency

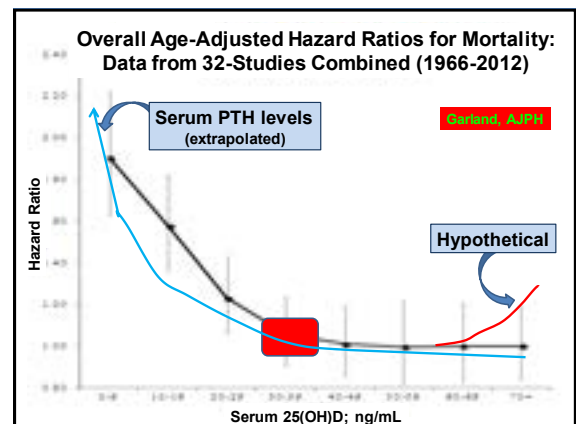
- Adults with vitamin D deficiency should be treated with 50,000 IU of vitamin D (or 8,000 IU a day), once a weeks for 6 – 18 weeks, with a maintenance dose between 1,000 and 2,000 IU per day.
- Those with GI malabsorption, metabolic syndrome, obesity, and DD patients may require 4,000 to 6,000 IU a day to maintain their serum 25(OH)D levels above 30 ng/mL

Wimalawansa, S.J., Current Osteoporosis Research, 10:4-15, 2012

Outcomes of Vitamin D, Must be Linked to Blood 25(OH)D Levels

- GI absorption of vitamin D varies among individuals. Thus, oral doses cannot accurately predict serum levels to be achieved
- Therefore, clinical studies should be designed to achieve a minimum target 25(OH)D level, than simply giving standard doses of vitamin D given to treated groups
- Then the outcomes can be standardize and interpret meaningfully

Wimalawansa, S.J., 2010



A Patient with Vitamin D Deficiency

Let's Look at a patient with developmental disability, vitamin D deficiency and how we could evaluate and manage this patient

60-Year Old Pt. with Down Syndrome

- Has a history of a fragility fracture, serum 25 hydroxy vitamin D is 12 ng/mL, and has low bone mineral density (DXA).
- DXA T score of - 3.0; read as "osteoporosis"; His bone alkaline phosphatase is three times the upper limit of normal.
- Is it possible that vitamin D (and calcium) alone could improve his BMD density on follow up DXA testing; (YES) OR.
- He should be treated with anti osteoporosis therapy? (most probably NOT)

60-Yr Old Pt. with Down Syndrome

- DXA testing cannot be done in 20 to 40% of DD patients (e.g., uncooperative, etc.). Even though he/she may be at high risk for fracture.
- Physician decided to treat a pt. with vitamin D alone, and patient's serum vitamin D level brought to the target, 40 ng/mL, but could not obtain a baseline or follow-up DXA.
- If the bone alkaline phosphatase became completely normal would that be a sufficient reason to hold off starting a bone pharmaceutical?

Take Home Messages

- Majority of such patients has an element of osteomalacia. Thus, the first action should be to correct vitamin D deficiency.
- If such a patient is to be treated with a potent anti-osteoporosis, patient must be treated first with Vit. D. Otherwise, patient is likely to get worse (harmed).
- Vast majority of these patients, the BMD improve toward normality with calcium and vitamin D supplements alone.
- Other co-morbidities will also improve

60-Yr Old Pt. with Down Syndrome

- When managing this patient with high risk for further fractures, you were not able to obtain a DXA testing, not even the baseline.
How do you manage that patients?
- Any additional bone turnover markers would help? NO
- Does anti-osteoporosis medications indicated? Most probably NOT

Summary

- Vitamin D deficiency is very common among the DD population
- These can be corrected with minimal cost, but with major benefits to our patients
- Recommended target to achieve is serum 25(OH)D levels between 40 and 60 ng/mL
- Those who are deficient needs loading (high) doses to achieve the target levels, and then a suitable maintenance doses.



Conclusions

Routine supplementation with vitamin D have a role in the **prevention** of a verity of common disorders affecting the DD patients; They are at **high-risk** for **vitamin D deficiency-associated complications**



Vitamin D Deficiency:

Perhaps the most cost-effectively preventable disease in the world

Quiz 2: What Serum 25(OH)D level Determine Vitamin D Insufficiency in Patients with Developmental Disability?

- A. **Less than 40 ng/mL**
- B. **More than 40 ng/mL**
- C. **Less than 20 ng/mL**
- D. **Less than 10 ng/mL**

Normal Range of serum 25(OH) Vitamin D:

Patients with Developmental Disability (and any institutionalized patient) the preferred (normal) range of serum vitamin D levels to optimize health is: **40 to 60 ng/mL**

For most patients, this requires supplementation of vitamin D between 2,000 and 4,000 IU a day

Thank you...

Sanil
Wimalawansa



**Vitamin D:
Everything You Need to Know**

by

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