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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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

Sunil Wimalawansa, MD, PhD, MBA
FACE, FACP, FRCP, FRCPath, DSc

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 Disability

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"
Consequences of Vitamin D Insufficiency

- Inadequate Vitamin D
- Decreased GI Calcium Absorption
- Increased GI absorption of calcium
- Increased renal Ca retention
- Increase osteoclast-mediated bone resorption
- Hypocalcemia
- Increased PTH levels in blood
- Increase PTH levels in blood
- Increase 1α-hydroxylase activity
- Converts 25(OH)D to 1,25(OH)2D
- Thus, even though 1,25(OH)2D is normal 25(OH)D may be low
- Thus, for vitamin D adequacy, 25(OH)D should be measured: Not 1,25(OH)2D

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

Prevalence of Vitamin D Deficiency in Healthy Adults (Boston)


Vitamin D [25(OH)D] Adequacy in General Population

The Vitamin D Continuum

- Deficiency
- Insufficiency
- Optimal
- ~20 ng/mL (50 nmol/L)
- 30 ng/mL (75 nmol/L)
- Optimal ~40 - 60 ng/mL

Wimalawansa, SJ. 2009

Serum 25(OH)D Levels in Patients with Developmental Disability

The Vitamin D Continuum

- Deficiency
- Insufficiency
- Optimal
- ~30 ng/mL (75 nmol/L)
- 40 ng/mL (100 nmol/L)

Wimalawansa, SJ. 2009
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

Vitamin D Status: Terminology

<table>
<thead>
<tr>
<th></th>
<th>General Public ng/mL</th>
<th>For DD population ng/mL</th>
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<tbody>
<tr>
<td>Deficiency</td>
<td>&lt; 15</td>
<td>&lt; 29</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>15 – 29</td>
<td>30 – 39</td>
</tr>
<tr>
<td>Normal (lab) range</td>
<td>30 – 70</td>
<td>30 – 100</td>
</tr>
<tr>
<td>Preferred range</td>
<td>30 – 50</td>
<td>40 – 60</td>
</tr>
<tr>
<td>Intoxication</td>
<td>&gt; 150</td>
<td>&gt; 150</td>
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Who is Vitamin D Deficient? Everyone

Who Should be Screened for Vt. 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

Recommendation for Vt. 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

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

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

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.

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 1α-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.”

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.

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”

Examples of Granulomatus 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
- Do not synthesize vitamin D in the skin:
  - Being African-American or Asian
  - Having darker skin; Older age
  - Avoiding sun exposure
  - Scared 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”

Medications that Decrease levels of Serum 25(OH)D

- Most anti-seizure medications
- Glucocorticoids
- Most medications use for AIDs
- Anti-fungal (e.g., ketoconazol)
- Chlestryamine, 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
**Prevalence of Vitamin D Insufficiency by Ethnicity**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Percentage (%)</th>
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<tbody>
<tr>
<td>Average</td>
<td>20</td>
</tr>
<tr>
<td>African American</td>
<td>30</td>
</tr>
<tr>
<td>Hispanic</td>
<td>25</td>
</tr>
<tr>
<td>Asian</td>
<td>20</td>
</tr>
<tr>
<td>Whites</td>
<td>15</td>
</tr>
</tbody>
</table>

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

**Vitamin D Deficiency Exacerbate Many Common Disorders**

- Muscle Weakness
- Glucose Intolerance
- Asthma
- Cognitive Impairment
- Cancer
- Cardiovascular
- Hypertension
- Depression
- Bone Pain
- Rickets

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

Vitamin D Deficiency

- Metabolic Syndrome
- Insulin Resistance
- Diabetes
- Obesity
- Hypertension
- Hyperlipidemia
- Vitamin D Deficiency

“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

Improve Prevent

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

Structures of Pro-hormones: Vitamin D₂ and D₃

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


Vitamin D is Uncommon in Food Intake Low At All Ages


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

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

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

**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 D$_2$ ]

**Vitamin D Assays: Which one is Reliable?**

Assays available for vitamin D measurements:

- 25(OH)D: is the standard clinical measure
- Immunoassays: RIA & ELIZA measures total 25(OH)D, including 25(OH)D$_2$ and 25(OH)D$_3$
- HPLC and LC: MS:MS – Measure D$_2$ and D$_3$ 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

**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

**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

**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

**Overall Age-Adjusted Hazard Ratios for Mortality:**

- Data from 32-Studies Combined (1966-2012)

<table>
<thead>
<tr>
<th>Serum 25(OH)D: ng/mL</th>
<th>Serum PTH levels (extrapolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>Hypothetical</td>
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</table>


Wimalawansa, S.J., 2008

Wimalawansa, S.J., 2010

Wimalawansa, S.J., 2012

Holick MF. N Engl. 2007; 357: 266-81

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