Vitamin D in The 21th Century

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Disclosure

- Consultant: Ultragenyx, Alexion, Ferrings
- Research grant support: Ultragenyx, Shire, Amgen
- Clinical Trial: Ultragenyx, Amgen
- Scientific exchange program: Alexion
Outline

- Overview of vitamin D synthesis and action
- Definition of vitamin D deficiency and insufficiency
- The skeletal and non-skeletal effect of vitamin D
- Recommendation of vitamin D intake
Sources of Vitamin D

The “D” represents D2 or D3: Two forms of exogenous: Ergocalciferol (D2) and Cholecalciferol (D3)

Endogenous: UV light (only D3): UV B (Shorter wave length)

- Few natural food: oily fish, food fortified with vitamin D
- Supplementation: D2 and D3

Sources of Vitamin D

- Vitamin D2 is manufactured through the ultraviolet irradiation of ergosterol from yeast
- Vitamin D3 through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin.
Sun Exposure

• Exposure of arms and legs for 5 to 30 minutes (depending on time of day, season, latitude, and skin pigmentation) between the hours of 10 a.m. and 3 p.m. twice a week is often adequate.
Sunlight vs. Ultraviolet B Radiation

- Exposure to one minimal erythemal dose while wearing only a bathing suit is equivalent to ingestion of approximately 20,000 IU of vitamin D2.
- The skin has a great capacity to make vitamin D3, even in the elderly.
Sun Protection Factor (SPF)

- Duration of skin exposed to the sun and developed first degree burn
- Individual has a different SPF
- All sun block will block UVB
- Some will block UVA as well.
**24 OH enzyme (CYP24A1 gene)**

Mutation of CYP24A1 mutation can cause nephrolithiasis and hypercalcemia. Also could be one of the etiologies of idiopathic infantile hypercalcemia.

It could be familial or sporadic

The homozygous/ complete mutation in CYP24A1 gene is compatible with life in mice model.

Measurement of 24,25 OH2 Vitamin D level is an indirectly evaluation of this enzyme activity.

**Sources of Vitamin D from Food**
### Laboratory Data in Rickets

<table>
<thead>
<tr>
<th>Type</th>
<th>Calcium</th>
<th>Phosphate</th>
<th>Alkaline Phosphatase</th>
<th>Calcidiol</th>
<th>Calcitriol</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium deficiency</td>
<td>↓↓</td>
<td>↓</td>
<td>↑↑</td>
<td>N</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Phosphate deficiency</td>
<td>N, ↑</td>
<td>↓↓</td>
<td>↑↑</td>
<td>N</td>
<td>↑↑</td>
<td>N, ↓</td>
</tr>
</tbody>
</table>

#### Vitamin D Deficiency

- **Mild**
  - N, ↓
  - N↓
  - ↑
  - ↓
  - ↓
  - N
  - N

- **Moderate**
  - ↓
  - ↓
  - ↓
  - ↑
  - ↓
  - ↓
  - ↓
  - ↑
  - ↑

- **Severe**
  - ↓
  - ↓
  - ↓
  - ↓
  - ↓
  - ↓
  - ↓
  - ↓
  - ↑
  - ↑

#### Loss of function CYP27B1 (25OHD-1a-hydroxylase)

- ↓↓
- ↓↓
- ↓↓
- ↑↑
- N
- ↓↓
- ↑↑

#### Loss of function VDR (R resistance to calcitriol)

- ↓↓
- ↓↓
- ↓↓
- ↑↑
- N
- ↑↑
- ↑↑
- ↑↑

#### Loss of function PHEX (X-linked hypophosphatemic rickets)

- N
- ↓
- ↑
- N
- ↓
- N

*N: normal, ↓: low, ↑: high*
Definition and Prevalence of Vitamin D Deficiency

• Vitamin D deficiency is defined as a 25-hydroxyvitamin D level of less than 20 ng/ml (50 nmol/L).
• A level of 25-hydroxyvitamin D of 21 to 29 ng/ml (52 to 72 nmol/L) can be considered to indicate a relative insufficiency of vitamin D, and
• A level of 30 ng per milliliter or greater can be considered to indicate sufficient vitamin D.
• Vitamin D intoxication is observed when serum levels of 25-hydroxyvitamin D are greater than 150 ng/ml (374 nmol/L).

Also at risk were pregnant and lactating women who were thought to be immune to vitamin D deficiency since they took a daily prenatal multivitamin containing 400 IU of vitamin D
  - 70% took a prenatal vitamin,
  - 90% ate fish,
  - 93% drank approximately 2.3 glasses of milk per day

• 73% of the women and 80% of their infants were vitamin D–deficient (25-hydroxyvitamin D level, <20 ng per milliliter) at the time of birth.
Risk factors for low vitamin D

• Low/decreased sun exposure due to pollution
• Dark clothing
• Excessive use of sunscreen
• Little time spent outdoors
• Increased skin pigmentation
• Lack of prenatal care in pregnant woman
• Prolonged breast feeding
<table>
<thead>
<tr>
<th>Cause</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudohypoparathyroidism: deficiency of plasma calcium-responsive element binding protein</td>
<td>Causes reduced or no renal synthesis of 1,25-dihydroxvitamin D</td>
</tr>
<tr>
<td>Vitamin D-resistant rickets (VDR-dependent rickets type 2) — mutation of the gene for the vitamin D receptor</td>
<td>Causes partial or complete resistance to 1,25-dihydroxvitamin D</td>
</tr>
<tr>
<td>X-linked hypophosphatemic rickets — mutation of the gene for the X-linked hypophosphatemic receptor</td>
<td>Causes increased intracellular phosphorylation of the vitamin D receptor and decreased renal 1,25-dihydroxvitamin D 2+3,4,5,6,7,8,9,10</td>
</tr>
<tr>
<td>Acquired disorders</td>
<td></td>
</tr>
<tr>
<td>Tumours induced by transforming growth factor 2+ and possibly other phosphatases</td>
<td>Causes phosphatase, decreased intestinal absorption of phosphorus, hyperphosphatemia, and decreased renal 1,25-dihydroxvitamin D 2+3,4,5,6,7,8,9,10</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
<td>Causes increased levels of 1,25-dihydroxvitamin D 2+3,4,5,6,7,8,9,10</td>
</tr>
<tr>
<td>Grand mal epileptic seizures, convulsions, tabes dorsalis, and other neurological conditions</td>
<td>Causes increased levels of 1,25-dihydroxvitamin D 2+3,4,5,6,7,8,9,10</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Causes increased levels of 1,25-dihydroxvitamin D 2+3,4,5,6,7,8,9,10</td>
</tr>
</tbody>
</table>

*This is a list of disorders that cause an increase in 1,25-dihydroxvitamin D levels.*

Breast Feeding
Breast feeding

- Human milk contains little vitamin D (approximately 20 IU per liter), and women who are vitamin D deficient provide even less to their breast fed infants.

- Lactating women given 4000 IU of vitamin D3 per day not only had an increase in the level of 25-hydroxyvitamin D to more than 30 ng per milliliter but were also able to transfer enough vitamin D3 into their milk to satisfy an infant’s requirement.

The Important of Vitamin D

- Skeletal system
- Nonskeletal system
  - Immune function: autoimmune diseases and infection
  - Cardiovascular risk
  - Cancer: common cancers
Children:

- In utero and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities (osteopenia, Rickets) and may increase the risk of hip fracture later in life.
Adult:

- Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture.
• Osteomalacia can often be diagnosed by using moderate force to press the thumb on the sternum or anterior tibia, which can elicit bone pain.

• One study showed that 93% of persons 10 to 65 years of age who were admitted to a hospital emergency department with muscle aches and bone pain and who had a wide variety of diagnoses, including fibromyalgia, chronic fatigue syndrome, and depression, were deficient in vitamin D.
Osteoporosis and Fracture

• Approximately 33% of women 60 to 70 years of age and 66% of those 80 years of age or older have osteoporosis.

• It is estimated that 47% of women and 22% of men 50 years of age or older will sustain an osteoporotic fracture in their remaining lifetime.

• Chapuy et al. reported that among 3270 elderly French women given 1200 mg of calcium and 800 IU of vitamin D3 daily for 3 years, the risk of hip fracture was reduced by 43%, and the risk of nonvertebral fracture by 32%.

• A 58% reduction in nonvertebral fractures was observed in 389 men and women over the age of 65 years who were receiving 700 IU of vitamin D3 and 500 mg of calcium per day.

Muscle Strength and Falls

• Vitamin D deficiency causes muscle weakness.

• Skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function.

• Performance speed and proximal muscle strength were markedly improved when 25-hydroxyvitamin D levels
  – increased from 4 to 16 ng per milliliter (10 to 40 nmol per liter)
  – and continued to improve as the levels increased to more than 40 ng per milliliter (100 nmol per liter).
A meta analysis of five randomized clinical trials (with a total of 1237 subjects) revealed that

- increased vitamin D intake reduced the risk of falls by 22% (pooled corrected odds ratio, 0.78; 95% CI, 0.64 to 0.92) as compared with only calcium or placebo.

The same meta-analysis examined the frequency of falls and suggested that

- 400 IU of vitamin D3 per day was not effective in preventing falls,
- whereas 800 IU of vitamin D3 per day plus calcium reduced the risk of falls (corrected pooled odds ratio, 0.65; 95% CI, 0.4 to 1.0).
Brain, prostate, breast, and colon tissues, among others, as well as immune cells have a vitamin D receptor and respond to 1,25-dihydroxyvitamin D, the active form of vitamin D.

In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1α-hydroxylase.
Non-skeletal Actions of Vitamin D

- Directly or indirectly, 1,25-dihydroxyvitamin D controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis.

- It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation.

- One practical application is the use of 1,25 dihydroxyvitamin D3 and its active analogues for the treatment of psoriasis.
People living at higher latitudes are at increased risk for Hodgkin’s lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes.

Both prospective and retrospective epidemiologic studies indicate that levels of 25-hydroxyvitamin D below 20 ng per milliliter are associated with a 30 to 50% increased risk of incidence of colon, prostate, and breast cancer, along with higher mortality from these cancers.
Latitude, Vitamin D Deficiency and Cancer

Cancer

• In a study of men with prostate cancer, the disease developed 3 to 5 years later in the men who worked outdoors than in those who worked indoors.

• Pooled data for 980 women showed that the highest vitamin D intake, as compared with the lowest, correlated with a 50% lower risk of breast cancer.

• Children and young adults who are exposed to the most sunlight have a 40% reduced risk of non-Hodgkin’s lymphoma and a reduced risk of death from malignant melanoma once it develops, as compared with those who have the least exposure to sunlight.

Latitude, Vitamin D Deficiency and Chronic Disease

Autoimmune Diseases, Osteoarthritis, and Diabetes

• Living at higher latitudes increases the risk of type 1 diabetes, multiple sclerosis, and Crohn’s disease.

• Living below 35 degrees latitude for the first 10 years of life reduces the risk of multiple sclerosis by approximately 50%.
Autoimmune Diseases, Osteoarthritis, and Diabetes

- Several studies suggest that vitamin D supplementation in children reduces the risk of type 1 diabetes.
- Increasing vitamin D intake during pregnancy reduces the development of islet autoantibodies in offspring.
- For 10,366 children in Finland who were given 2000 IU of vitamin D3 per day during their first year of life and were followed for 31 years, the risk of type 1 diabetes was reduced by approximately 80% – relative risk, 0.22; 95% CI, 0.05 to 0.89.
- Among children with vitamin D deficiency the risk was increased by approximately 200% – relative risk, 3.0; 95% CI, 1.0 to 9.0.

In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome.

Another study showed that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes by 33% (relative risk, 0.67; 95% CI, 0.49 to 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D.
Cardiovascular Disease

- Living at higher latitudes increases the risk of hypertension and cardiovascular disease.

- In a study of patients with hypertension who were exposed to ultraviolet B radiation three times a week for 3 months, 25-hydroxyvitamin D levels increased by approximately 180%, and blood pressure became normal (both systolic and diastolic blood pressure reduced by 6 mm Hg).

- Vitamin D deficiency is associated with congestive heart failure and blood levels of inflammatory factors, including C-reactive protein and interleukin-10.

Schizophrenia and Depression

- Vitamin D deficiency has been linked to an increased incidence of schizophrenia and depression.

- Maintaining vitamin D sufficiency in utero and during early life, to satisfy the vitamin D receptor transcriptional activity in the brain, may be important for brain development as well as for maintenance of mental function later in life.
Lung Function and Wheezing Illnesses

- Men and women with a 25-hydroxyvitamin D level above 35 ng per milliliter (87 nmol per liter) had a 176-ml increase in the forced expiratory volume in 1 second.

- Children of women living in an inner city who had vitamin D deficiency during pregnancy are at increased risk for wheezing illnesses.

Vitamin D Requirements and Treatment Strategies
AAP replaced a 2003 clinical report which recommended a daily intake of 200 IU/day of vitamin D for all infants (beginning in the first 2 months after birth), children, and adolescents.

The new recommended daily intake of vitamin D is 400 IU/day for all infants, children, and adolescents beginning in the first few days of life.

Recommendations from the Institute of Medicine (IOM) for adequate daily intake of vitamin D are:
- 400 IU infant less than 2 month with breast feeding (AAP)
- 600 IU for children and adults up to 50 years of age,
  - 600 IU for adults 51 to 70 years of age,
  - 800 IU for adults 71 years of age or older.

However, most experts agree that without adequate sun exposure, children and adults require approximately 800 to 1000 IU per day.

Children with vitamin D deficiency should be aggressively treated to prevent rickets.
Vitamin D Requirements and Treatment Strategies in Children and Adults

• Since vitamin D2 is approximately 30% as effective as vitamin D3 in maintaining serum 25-hydroxyvitamin D levels, up to three times as much vitamin D2 may be required to maintain sufficient levels.

• A cost-effective method of correcting vitamin D deficiency and maintaining adequate levels is to give patients a 50,000-IU capsule of vitamin D2 once a week for 8 weeks, followed by 50,000 IU of vitamin D2 every 2 to 4 weeks thereafter. Daily 2000-4000 IU of Vitamin D intake is sufficient as well.

Vitamin D Supplement

• If a vitamin D supplement is prescribed, 25-OH-D levels should be repeated at 3-month intervals until normal levels have been achieved.

• PTH and bone-mineral status should be monitored every 6 months until they have normalized.
Vitamin D Intoxication

- Vitamin D intoxication is extremely rare but can be caused by inadvertent or intentional ingestion of excessively high doses.

- Doses of more than 50,000 IU per day raise levels of 25-hydroxyvitamin D to more than 150 ng per milliliter (374 nmol per liter) and are associated with hypercalcemia and hyperphosphatemia.
Summary

• 25 OH Vitamin D is a predictor for bone health and major store of Vitamin D in the body

• Keep 25 OH Vitamin D level above 30 ng/dl (Preferred 40-60 ng/dl)

• Wearing sunblock will prevent vitamin D synthesis

• Supplementation is NOT needed if there is an adequate sunlight exposure.

Summary

• Vitamin D has it’s skeletal and non- skeletal effect

• Vitamin D intoxication is not common unless taking an excessive amount or 24 OH activity is impaired

• Overall, the benefit of vitamin D intake outweighs the risk

• When treating not supplementing Vitamin D, the level of Vitamin D should be evaluated for proper treatment and adjust the dose if necessary
Start Your Vitamin D today

Thank You