Vitamin D

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Historical Milestones

Since 1918 when Rickets were first described being cured with cod liver oil in animals, vitamin D has been a topic of discussion as it related to general health. Through the last century, many of the key biochemical pathways involved in the processing, transformation and utilization of vitamin D have been discovered but the direct impact on the body's health had still eluded the medical community. In the 1970's vitamin D's relationship to calcium regulation was identified. The following 3 decades saw sporadic studies relating vitamin D to psoriasis and other immune system functions. The late 1990's and the early years of the 21st century saw an explosion of studies relating vitamin D to general health and specific disease entities such as osteoporosis with a feverish spread of information propagated by the lay press.

Metabolism and Physiology

But what is vitamin D and how does it affect the body? Unconverted vitamin D (cholecalciferol) is either formed in the skin with exposure to UV light or consumed via a variety of foodstuffs such as fish, eggs or supplements. It is removed from circulation within hours. Cholecalciferol is best absorbed from gut when ingested with lipids, absorbed passively in the small intestine and transported to the liver then to target tissues via the carrier protein vitamin D binding protein (transcalciferin)

In the liver cholecalciferol is converted to the stable form of vitamin D known as 25(OH)D (calcidiol; 25-hydroxycholecalciferol) which re-enters the circulation within a few hours. The most abundant of all vitamin D metabolites, 25(OH)D is the best metabolite to measure for assessment of vitamin D nutritional status having the longest half life of approximately 3 weeks.

The primary function of vitamin D is preservation of serum calcium levels. Calcium is the most abundant mineral in body. It stabilizes cell membranes and controls membrane excitation in nerve and muscle necessary for muscle contraction. Calcium plays a role in intercellular adhesion, activation of plasma clotting enzymes, release of hormones into the blood, and is a basic constituent of bone and teeth (calcium phosphate).

Facilitated by parathyroid hormone (PTH), in the kidney 25(OH)D is converted to 1,25(OH)D3 (calcitriol; 1,25-dihydroxycholecalciferol). In this form, no longer a vitamin but now a hormone, it controls and regulates the activity of cells and/or organs via a nuclear receptor (VDR: vitamin D receptor) to

- Promotes absorption of calcium and phosphorus from intestine
- Increases reabsorption of phosphate in kidney
- Acts on bone to release calcium and phosphate
- Facilitates osteoid calcification (bone formation)

Parathyroid hormone (PTH), like vitamin D, acts to preserve serum calcium concentration by increasing 1,25(OH)D and decreasing serum phosphorus (preventing its binding to calcium). Elevated serum calcium levels will increase the conversion of 1,25(OH)D to the inactive form 1,24,25(OH)D which is excreted via the kidneys.

In recent years, other than balancing mineral metabolism, vitamin D's influence in >50 genes has been confirmed leading to the discovery of numerous non-classical roles for vitamin D including:

- **Promoting immunity:** infectious agents cause the VDR to be increased on infection fighting cells such as macrophages. 25(OH)D is then able to attach and increase intracellular 1,25(OH)2D production which is released locally and acts on activated T-lymphocytes to regulate cytokine synthesis as well as activated B-lymphocytes to regulate immunoglobulin synthesis
- **Blood pressure regulation:** acts on the kidney to decrease renin production
- **Blood glucose control:** promotes increased insulin secretion from the pancreas
- **Cancer risk reduction:** many cancers
- **$1,25(OH)_2D$** in tissues regulates proliferation genes p21 and p27, inhibits angiogenesis genes and induces differentiation and apoptosis
- **Cell differentiation:** direct effect on various nuclear receptors in prostate, liver, thyroid, and brain. These influences may lead to new therapeutic treatments specifically targeting cells using 1,25(OH)D3

Cancer	**Musculoskeletal**	**Inflammatory/ Autoimmune**
Colon cancer	Myalgia	Multiple sclerosis
Breast cancer	Fractures	Vitiligo
Ovarian cancer	Osteopenia	SLE
Bladder cancer	Osteoporosis	Newborn respiratory infections
Esophageal cancer	Osteoarthritis	IBD / Chron's
Cervical cancer	Fibromyalgia	Psoriasis
Uterine cancer	Rickets	Senile warts
	Rheumatoid arthritis	Tuberculosis
Neurologic	**Cardiovascular**	**Endocrine**
Parkinson's	Hypertension	Diabetes
Schizophrenia	Arteriosclerosis	Thyroiditis
Seasonal affective disorder	Myocardial infarct	Obesity
Autism		Pancreatitis

From ape to the hunter-gatherer cave man to the modern day office, evolutionary changes have altered how humans receive and produce vitamin D. The amount of time and skin surface exposed to the sun has decreased significantly. Thus, limiting the amount of vitamin D produced in the skin. Darker skin tones, the use of sunscreen and higher latitudes from the equator further limit the production of vitamin D in the skin.

Vitamin D Deficiency

U.S. intake is only 30% of current recommended daily allowance, which itself is considered too low for normal functions. It is estimated that 1 billion people worldwide are vitamin D deficient or have insufficient levels. This includes

- >50% postmenopausal women on medications for osteoporosis
- 41% of African American women 15-49 years old
- 40-100% of elderly (US/Europe)
- >60% of those >70 year old (have a 50% decrease in skin synthesis)
- Breast fed babies (low quantity)
- Vegans (low quantity)
- Alcoholics (decreased absorption)
- Smokers (increased bone turnover; higher levels needed)
- Obese individual (increased storage, decreased availability)

Cause	Effect
Reduced Skin Synthesis (environment)	
Sunscreen use	Reduces D_3 – SPF8: 92.5%; SPF15: 99%
Skin pigment blocks UVB	Reduces D_3 by 99%
Aging	Reduces D_3 by 75% in a 70 year-old
Season, latitude, time of day	Above 35° latitude (Atlanta) = no D_3 produced Nov-Feb
Skin graft (decreased 7-dehydrocholesterol)	Reduced D_3 production
Decreased Bioavailability	
Malabsorption	Impaired vitamin D uptake
Obesity - sequestration in body fat	Reduces availability of vitamin D
Breast feeding	Poor content in breast milk; needs supplementation
Increased Catabolism	
Anticonvulsants, HIV treatment	Increases inactivation to the 24(OH) form
Nephrotic syndrome	Increased loss of 25(OH)D bound to DBP in urine
Decreased Synthesis	
Liver failure [decreased 25(OH)D]	Varies from malabsorption to lost production
Chronic renal disease [decreased 1,25(OH)D]	Low phosphorus decreases 1-hydroxylase enzyme available Decreased $1,25(OH)_2D$ production Hypocalcemia, secondary hyperparathyroidism

The vitamin D system maintains calcium levels as a priority. During periods of deficiency or insufficiency, the paracrine control via 1,25(OH)2D that tissues need to function properly is severely limited. Deficiency of Vitamin D results in many physiologic changes including:

- Failure of bone formation in a growing person (rickets)
- Failure of bone to calcify in adults (osteomalacia)
- Thinning of bone due to loss of calcium and protein (osteoporosis)
- Decreased serum calcium levels
- Decreased serum and intracellular 1,25(OH)2D levels
- Stimulation of excess parathyroid hormone (PTH) production further reducing calcium in bone

So how do we increase our vitamin D levels given human current evolutionary environmental status? Eating a healthy diet is a start. However, that may not be enough in most individuals and supplementation may be needed. There are two main forms of vitamin D, D2 and D3. Both forms have similar absorption rates and increase serum 25(OH)D levels. D3 has been shown in some studies to be more effective at maintaining 25(OH)D levels; however, other studies suggest they are equal and that it is the carrier media (i.e., ethanol vs oil vs lactose) that has an influence on the bioavailability and/or catabolism of these molecules. Overall, the D3 form has a higher affinity for the various receptors and carriers in the body. D3 is not directly metabolized to inactive 24(OH)D form as is D2 and D2 shows a greater paradoxical decrease in total 25(OH)D during high-dose treatment than does D3. Regardless of source or supplementation form, total vitamin D testing should measure total vitamin 25(OH)D, both D2 and D3.

Source	Amount (IU)	D - type Content
Natural Sources		
Salmon (3.5 oz)	100-1000	D3
Sardines (3.5 oz)	300	D3
Mackerel (3.5 oz)	250	D3
Tuna (3.6 oz)	230	D3
Cod Liver Oil (1 tsp)	400-1000	D3
Shitake Mushrooms (3.5 oz)	100-1600	D3
Egg Yolk	20	D3 or D2
Sunlight (0.5 Min Erythema Dose)	3,000	D3
Fortified Foods		
Fortified Milk	100	D3
Fortified Orange Juice	100	D3
Infant Formulas	100	D3
Fortified Yogurts	100	D3
Fortified Butter	50	D3

Fortified Margarine	430	D3
Fortified Cheeses	100	D3
Fortified Cereals	100	D3
Supplements		
Prescription D2 (ergocalciferol)	50,000	D2
Drisdol (D2 liquid capsules)	8,000	D2
OTC Multivitamin	400	D, D2, D3
OTC Vitamin D3	400-2,000	D3

Blood Levels: Key Metabolites

The best measure of vitamin D status is 25(OH)D. Vitamin D levels vary greatly depending on age, diet and latitude! Reviews, opinions and interpretations vary for an appropriate 25 (OH) D range:

- Literature (2000-2010): 30-60 ng/mL
- IOM (November 2010): > 20 ng/mL

Institutes of Medicine Recommendations (Nov 2010)

Dietary Reference Intakes for Calcium and Vitamin D						
	Calcium			**Vitamin D**		
Life Stage Group	**Estim Avg Req'd (mg/day)**	**Upper Level Intake (mg/day)**	**RDA (mg/day)**	**Estim Avg Req'd (IU/day)**	**Upper Level Intake (IU/day)**	**RDA (IU/day)**
Infants 0-6 months	*	*	1000	**	**	1000
Infants 6-12 months	*	*	1500	**	**	1500
1-3 years	500	700	2500	400	600	2500
4-8 years	800	1000	2500	400	600	3000
9-13 years	1100	1300	3000	400	600	4000
14-18 years	1100	1300	3000	400	600	4000
19-30 years	800	1000	2500	400	600	4000
31–50 years	800	1000	2500	400	600	4000
51–70 year, males	800	1000	2000	400	600	4000

51–70 year, females	**1,000**	**1200**	**2000**	**400**	**600**	**4000**
>70 years	**1,000**	**1200**	**2000**	**400**	**800**	**4000**
14–18 years, pregnant/lactating	**1,100**	**1300**	**3000**	**400**	**600**	**4000**
19–50 years, pregnant/lactating	**800**	**1000**	**2500**	**400**	**600**	**4000**
*For infants, Adequate Intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age. **For infants, Adequate Intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age.						

Why Measure 25(OH)D? Serum 25(OH)D is relatively stable (25 day half-life) and not directly influenced by dietary calcium intake and life style (eg, immobility of elderly or infirmed). Measurement of 25(OH)D levels is done to assess vitamin D deficiency/insufficiency in various clinical situations:

- Nutritional status assessment (immigrants, pregnant women)
- Malabsorption (older persons)
- Nephrotic syndrome
- Diagnosis of rickets (young children)
- Osteoporosis (older persons)
- Decreased 25-hydroxylation (liver disease)
- Monitor treatment efficacy
- Vitamin D intoxication (clinical hypercalcemia) in which 25(OH)D is high and 1,25(OH)D is normal

Measuring 1,25(OH)D is generally not recommended to assess vitamin D status because it is kept within reference limits as long as possible by hormonal mechanisms, levels are decreased severe vitamin D deficiency as they are substrate [25(OH)D] dependent and the half-life is very short (7 hours). Measurement is recommended in certain clinical situations such as

1. Disorders of 1-hydroxylation [↓ levels 1,25(OH)D]
   - Renal failure
   - Vitamin D – dependent rickets type 1
   - Hypophosphatemic rickets
   - HIV protease inhibitors
2. Vitamin D receptor defects [↑ levels 1,25(OH)D]
   - Vitamin D–dependent rickets type 2 in which there is vitamin D resistance/insensitivity
3. Extrarenal 1-hydroxylation [hypercalcemia + ↑ 1,25(OH)D]
   - Sarcoidosis, tuberculosis, rheumatoid arthritis
   - Inflammatory bowel disease
   - Lymphoproliferative disease

Signs and symptoms of vitamin D toxicity include loss of appetite, excessive thirst, nausea and vomiting. Studies have shown that given the current recommended daily allowances and the capacity of DBP to bind vitamin D and its metabolites toxicity seems an extremely low occurrence. Acute vitamin D intoxication has been reported in children associated with over-the-counter supplement that belonged to their parents.

Summary

Vitamin D deficiency is very common in industrialized societies. There is variation on what is an optimal level of 25(OH)D. The IOM recently released their updated recommendations; however numerous studies show that 400 IU of vitamin D is not enough to compensate for typical lack of exposure to sunlight in modern society and the use of sunscreen to prevent skin cancer. Measuring total 25(OH)D (not the individual products) is the best way to monitor vitamin D status. Supplementation may be necessary in many individuals. The D3 form has slightly better properties; however, either when taken in appropriate dose will support a 25(OH)D level that will assist the body in maintaining calcium level homeostasis.