Functional Medicine University's Functional Diagnostic Medicine Training Program

Module 7 * FMDT 563E

Physiology of the Parathyroid Glands

(Vitamin D Metabolism and Assessment)

By Wayne L. Sodano, D.C., D.A.B.C.I.
http://www.FunctionalMedicineUniversity.com

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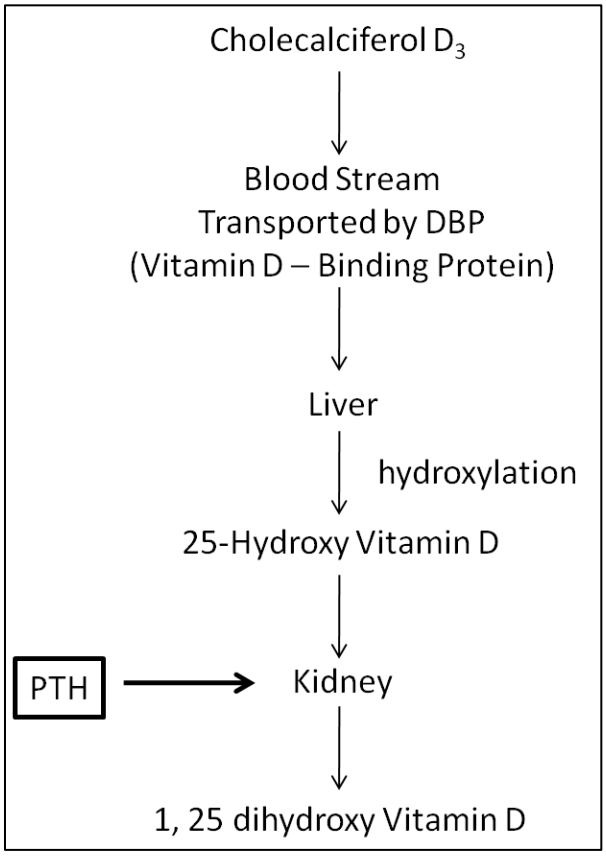
Contents

The four parathyroid glands are located on the posterior side of the thyroid gland. Each parathyroid gland is about 6mm long, 3mm wide and 2mm thick.[1] The parathyroid glands have two basic type of cells: chief cells and oxyphil cells. The chief cells are responsible for secreting parathyroid hormone (PTH). Parathyroid hormone is the most important endocrine regulator of calcium and phosphorus in extracellular fluid.

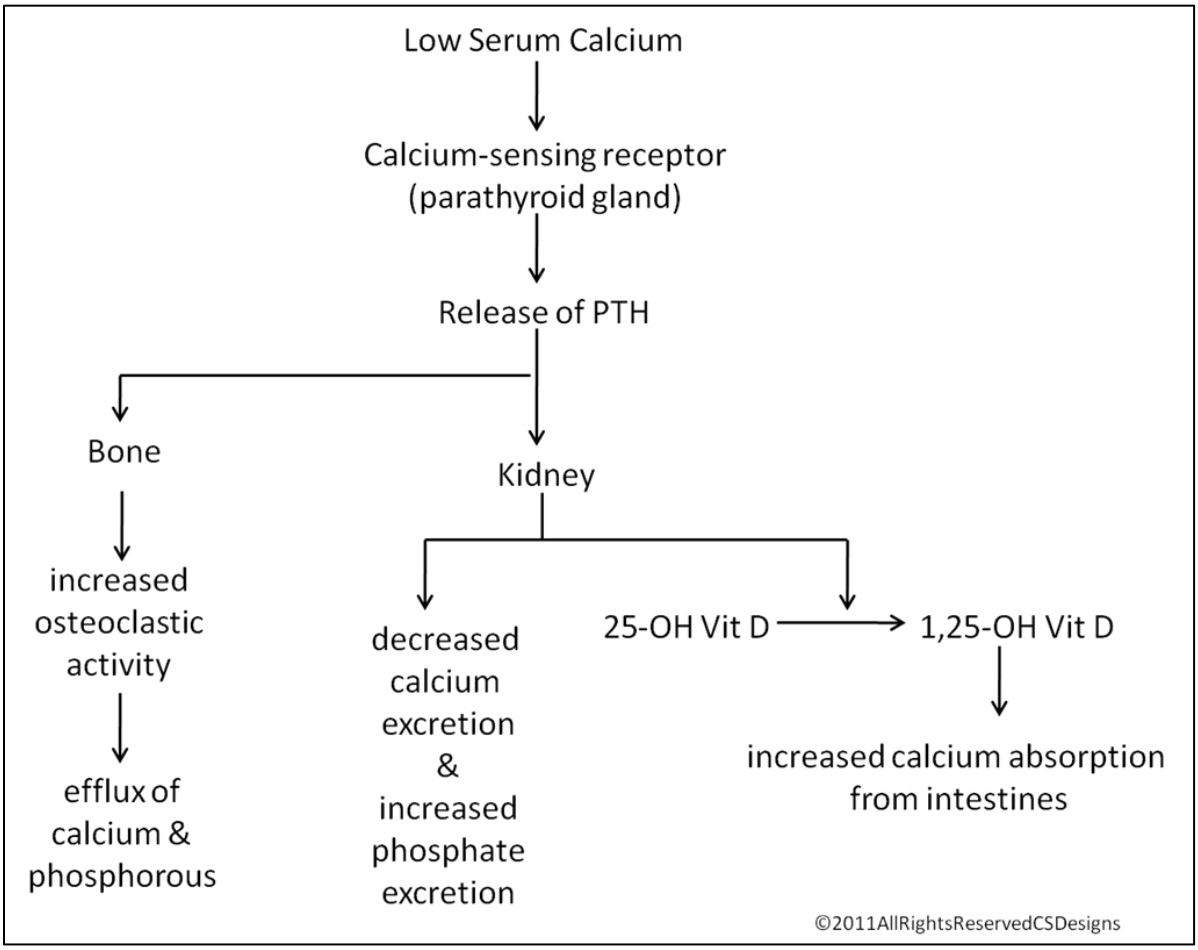
The Physiological Effects of PTH

- Increases calcium and phosphate absorption from bone (activation of osteoclasts)
- Decreases calcium excretion and increases phosphate excretion by the kidneys (increases renal reabsorption of calcium at the same time diminishes phosphate reabsorption)
- Increases intestinal absorption of calcium and phosphate (indirectly by increasing the formation in the kidneys of 1,25-dihydroxycholecalciferol)

The decline in phosphate concentration is caused by a strong effect of PTH to increase renal phosphate excretion, an effect that is usually great enough to override increased phosphate absorption form the bone.[1]



The Control of Parathyroid Hormone Secretion



Parathyroid hormone is released in response to low extracellular concentrations of calcium ions. The parathyroid cells have receptors that monitor extracellular calcium ion concentration. These receptors are appropriately called calcium-sensing receptors. The calcium-sensing receptor (CaSR) represents the molecular mechanism by which parathyroid cells detect changes in blood ionized calcium concentration and modulate PTH secretion to maintain serum calcium levels within a narrow range. CaSR also influences both gene transcription and cell proliferation in parathyroid cells.[2]

Hypoparathyroidism

Hypoparathyroidism is a condition that causes a decrease in secretion of parathyroid hormone. A decrease in PTH leads to low serum calcium and high serum phosphorous. The most common cause of hypoparathyroidism is a loss of parathyroid tissue due to surgery of the thyroid or parathyroid. Other causes include: autoimmune disease (associated with Addison's disease), and hypomagnesemia.

Functional hypoparathyroidism can occur as a result of magnesium deficiency, which prevents the secretion of PTH. Calcium and magnesium are closely related. When magnesium level is low, calcium level may also decline. Magnesium is often cited as one of the most deficient elements in modern diet.[3] Magnesium is involved with the active transport of other ions. The antihypertensive effects of magnesium may be related to its involvement in moving calcium out of the cell, allowing smooth muscle dilatation.[3]

A rare cause of hypoparathyroidism is known as pseudo-hypoparathyroidism or resistance to parathyroid hormone. In this condition, the kidneys and the bones do not respond to PTH. Serum PTH level will generally be normal or slightly elevated in pseudo-hypoparathyroidism.

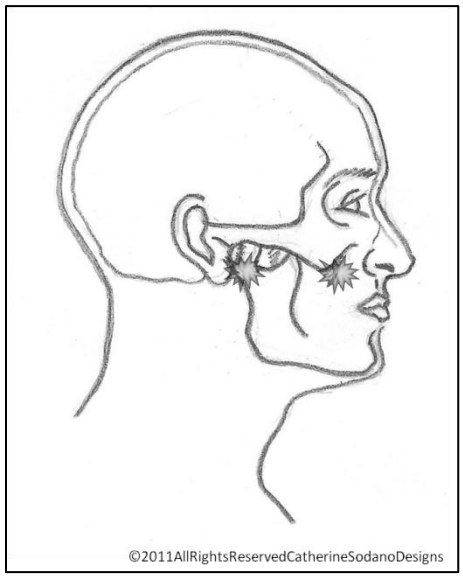
[Hypomagnesemia may be seen in malabsorption syndromes, malnutrition, parathyroid disorders, chronic alcoholism, chronic diarrhea, long term use of proton pump inhibitors, renal disorders, diabetes(due to glucose-induced dieresis secondary to poor glucose control), and pregnancy.]

NOTE: Keep in mind that hypocalcemia can be due to hypomagnesemia

Signs and Symptoms of Hypoparathyroidism

- Brittle nails
- Dry hair
- Tingling in the lips, fingers, and toes
- Muscle cramps/spasms
- Fatigue and/or weakness
- Painful menstruation
- Change in mental status

Physical Exam Testing for Hypocalcemia



Chvostek's sign

Procedure: Tap on the facial nerve just anterior to the ear and just below the zygomatic arch.

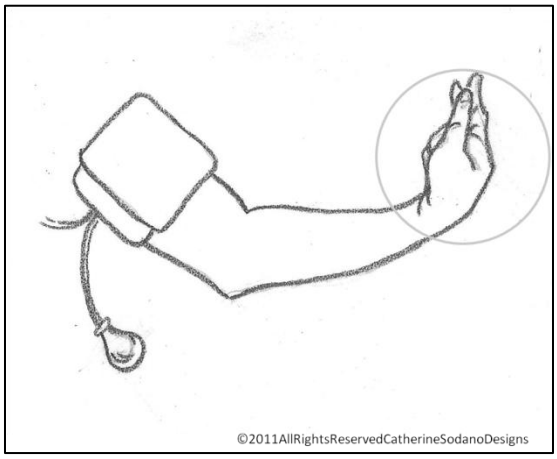
Positive Response: Twitching of the ipsilateral facial muscles (this is suggestive of neuromuscular excitability
caused by hypocalcemia).

Trousseau's sign

(Trouseau's sign is believed to be more specific for hypocalcemia than Chvostek's sign.[4]

Procedure: Inflate a blood pressure cuff to a pressure above the patient's systolic level. Keep inflated for several minutes.

Positive Response: Flexion of the wrist and metacarpophalangeal joints, extension of the fingers and adduction of the thumb.



Hypoparathyroidism: Lab Testing

- Low serum calcium
- High serum phosphorus
- Low serum magnesium
- Low parathyroid hormone
- Alkaline phosphatase is usually normal
- Decreased 1, 25-dihydroxycholecalciferol (the conversion of 25-hydroycholecalciferol to the active form on vitamin D, 1, 25-dihydroxycholecalciferol requires PTH)

Serum Calcium

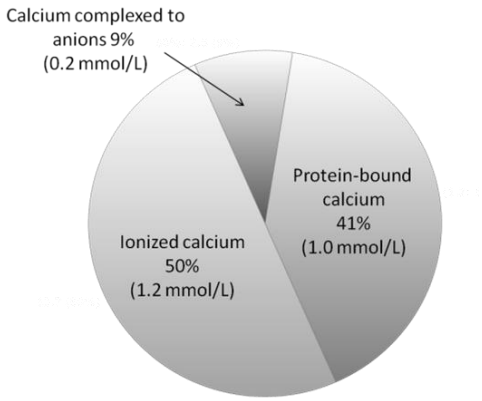
It's important to remember that serum calcium exists in three forms:

1. Protein-bound calcium – 41%
2. Ionized calcium – 50% (diffusible through the capillary membrane)
3. Calcium complexed to anions, such as citrate and phosphate – 9% (non-ionized is diffusible through the capillary membrane)

The ionic form of calcium is the functional form of calcium that is involved with heart function, nervous system functions and bone formation. Calcium's actions are wide ranging as neuronal excitation, hormonal secretion, neurotransmitter release, innate immunity, and muscle tone of smooth muscle cells of the vasculature, airways, uterus, gastrointestinal tract, and urinary bladder.[3]

Since a good portion of serum calcium exists bond to protein, mainly albumin, you will need to check the serum albumin level when assessing serum calcium status. In the case of hypoalbuminemia, serum calcium needs to be correct in order to obtain the true value. See below for calcium correction formula.

Corrected serum calcium mg/dL = serum calcium mg/dL + (0.8 x [4.0 – albumin g/ml])



Hyperparathyroidism

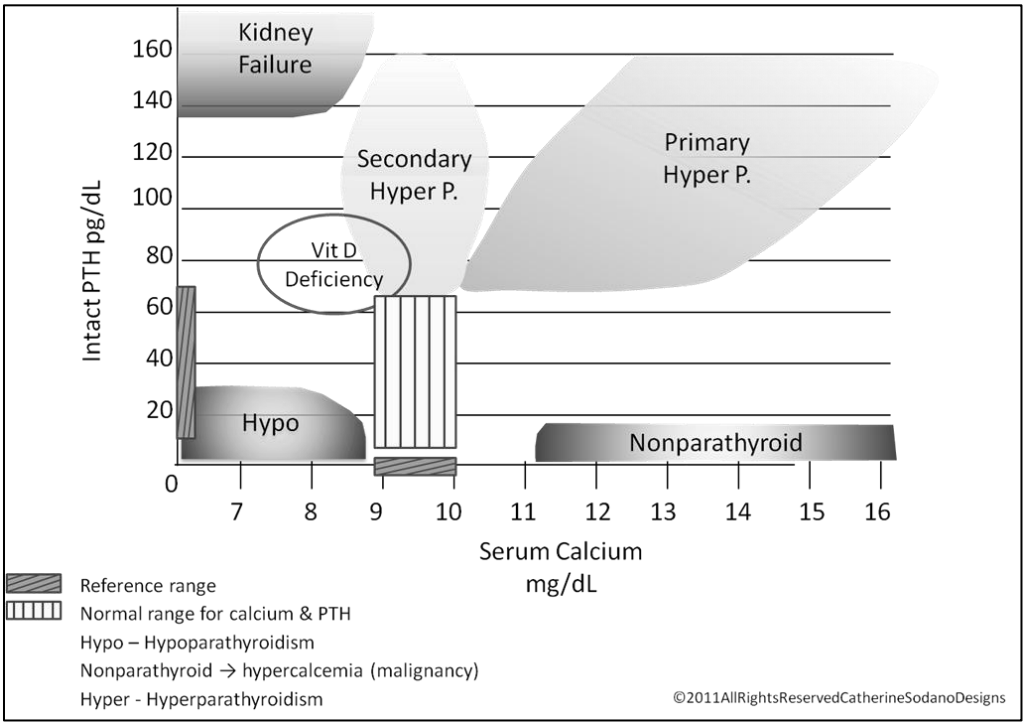
The hypercalcemia of hyperparathyroidism is typically discovered accidentally by routine chemistry panels. [5] Hyperparathyroidism is caused by hypersecretion of PTH, which can be cause by primary or secondary conditions. In primary hyperparathyroidism, the most common cause is a single parathyroid adenoma (80%) and less commonly by hyperplasia by two or more parathyroid glands (20%), or carcinoma (< 1%).[5] When hyperparathyroidism presents before age 30, there is a higher incidence of multiglandular disease and carcinoma. **The hallmark of primary hyperparathyroidism is a serum calcium level greater than 10 mg/dL.** Serum phosphate is usually low and presents at a value of less than 2.5 mg/dL.

Secondary hyperparathyroidism occurs as a compensation for hypocalcemia rather than as an abnormality of the parathyroid glands. This contrasts with primary hyperparathyroidism, which is associated with hypercalcemia.[1] Secondary hyperparathyroidism can also be caused by vitamin D deficiency. Serum calcium is typically normal, but may elevate with time due to parathyroid gland hyperplasia.

Signs and Symptoms of Hyperparathyroidism

- Bone pain – especially the legs and arms
- Kidney stones
- Fatigue
- Hypertension
- Recurrent headaches
- Constipation
- Polyuria
- Mental changes

PTH and Serum Calcium Nomogram



Drug Induced PTH Changes

Drugs that may increase PTH level:

- Phosphates
- Anticonvulsants
- Steroids
- Isoniazid (used to treat TB)
- Lithium
- Rifampin (used to treat TB)

Drugs that may decease PTH level:

- Cimetidine (Tagamet)
- Propranolol

Parathyroid Treatment Considerations

- Primary hyperparathyroidism requires a referral to a qualified physician
- Secondary hyperparathyroidism- correct vitamin D deficiency. For patients with chronic kidney disease, consult with qualified physician
- Hypoparathyroidism – assess for calcium, magnesium and vitamin D, and treat accordingly. Remember that magnesium is best assessed by testing red blood cell level. Encourage your patient to eat calcium rich foods, and to avoid foods and drinks with high phosphorus content. Assess for GI, liver, immune and renal dysfunction, and treat accordingly. Reassess blood chemistry frequently during treatment.

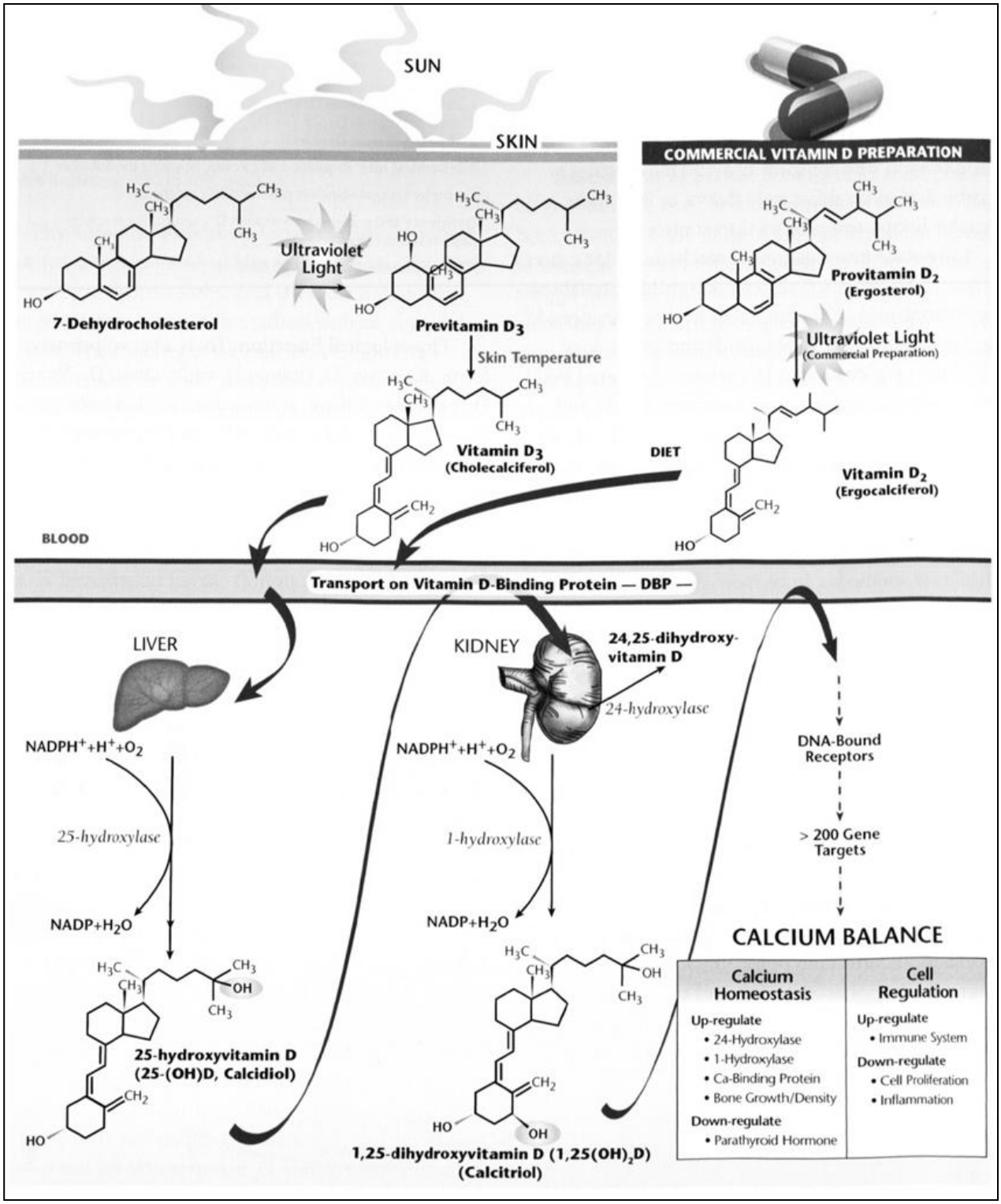
Vitamin D

Vitamin D is a fat-soluble vitamin that functions as a hormone precursor (pro-hormone). As techniques of genomics, proteomics and molecular biology continue to rapidly advance, the research on vitamin D and other nutrients has evolved from strictly nutritional toward transcription gene regulation, translational and post-translational, and receptor-mediated effects.[6] There are two primary forms of vitamin D:

1. Vitamin D_3 (cholecalciferol) – Obtained from the diet (found in fish, egg yolk, beef liver and cheese), and synthesized in the skin from 7-Dehydroxycholesterol after exposure to UV light (UVB) from the sun.

2. Vitamin D_2 (ergocalciferol) – produced by irradiation of ergosterol (provitamin D_2), a sterol found in fungi. Ergocalciferol is also used in commercial vitamin D preparation (supplements). [Vitamin D_2 undergoes reactions similar to the D_3 pathway. It goes from ergosterol, to ergocalciferol, to 25-hydroxyvitamin D_2 and then to the final active form 1, 25-dihydroxyvitamin D_2.][3] Vitamin D_3 is more potent, more stable, and binds more efficiency to Vitamin D binding protein than vitamin D_2.

Activation of Vitamin D



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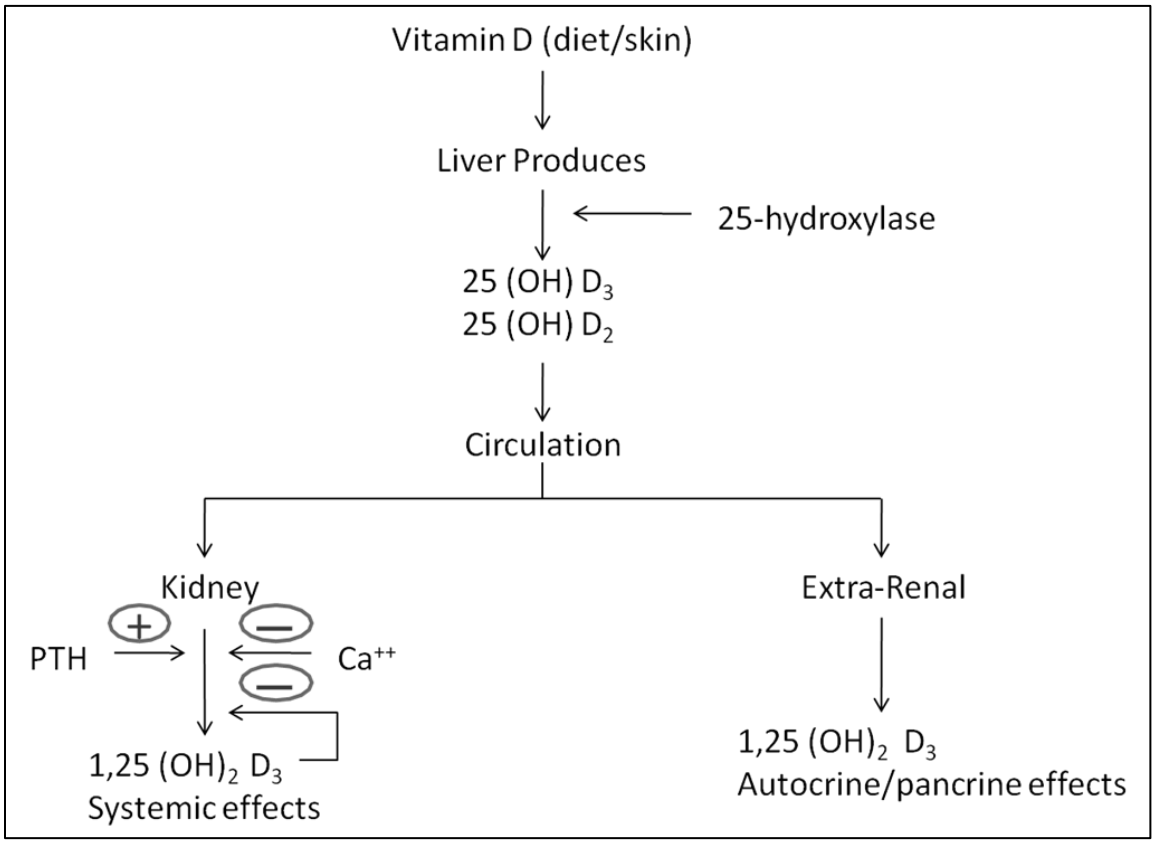
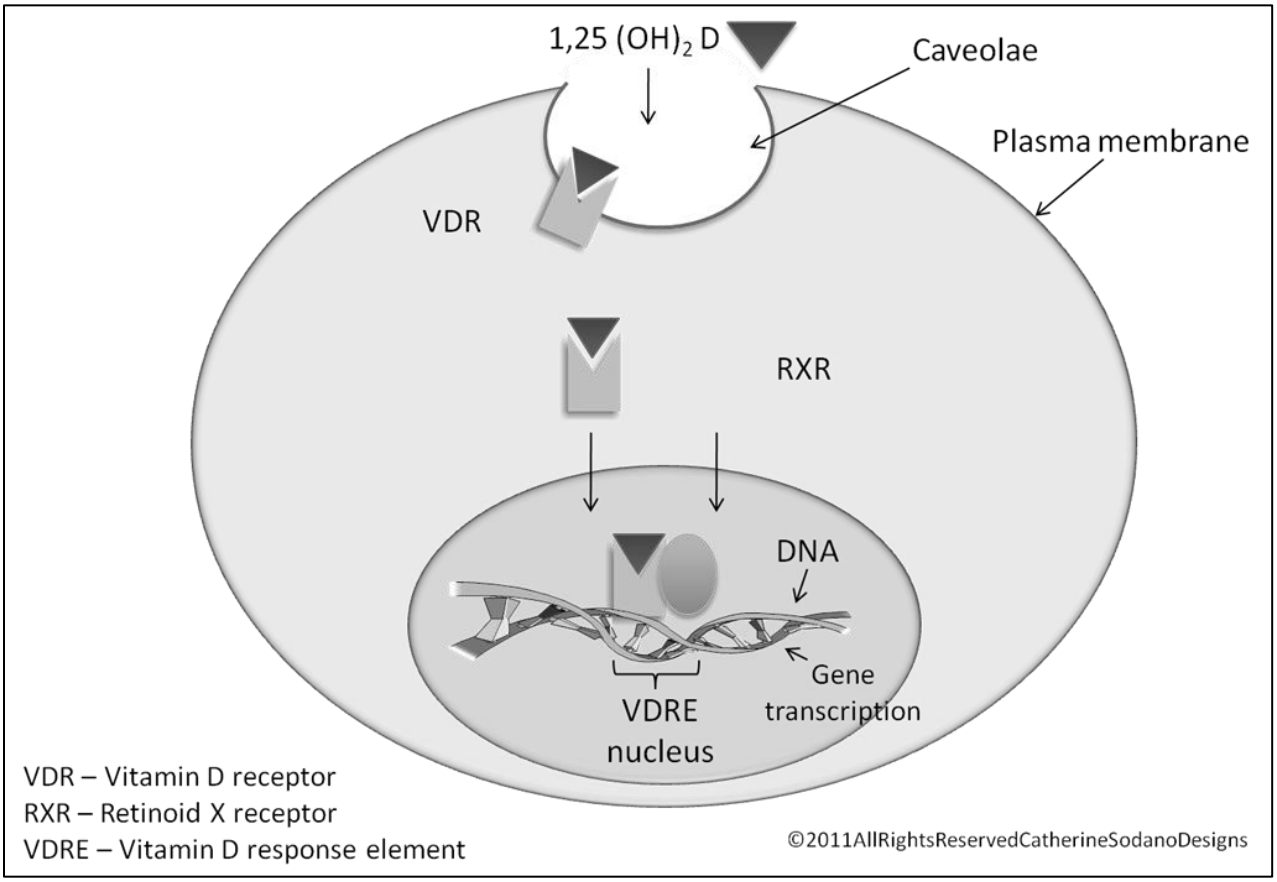
Vitamin D itself is biologically inactive, and it must be metabolized to its biologically active forms. Circulating vitamin D_3 and D_2 enter the liver where they are acted upon by 25-hydroxylase (CYP27A1). This liver enzyme converts vitamin D_3 and D_2 to 25(OH) D_3 and 25(OH) D_2. These 25(OH) D molecules are circulated to the kidney, where another cytochrome-type 1alpha-hydroxylase enzyme (CYO27B1) performs another hydroxylation, producing 1 alpha, 25-dihydoxyvitaminD_3 (also called; calcitiol and 1, 25$(OH)_2$ D).[7] This is the active form of vitamin D.

Synthesis of 1, 25-dihydroxycholecalciferol
(Active form of Vitamin D)



Mechanism of Action



Most of the actions of vitamin D are mediated through a nuclear transcription factor known as vitamin D receptor (VDR). 1, 25 $(OH)_2$ D combines with the VDR in an area of the cell plasma membrane called the caveolae. The VDR will combine with the retinoic acid X receptor to form a heterodimer that binds to the vitamin D response element on the DNA. This interact initiates a cascade of molecular interacts that modulates (i.e. activates or deactivates) transcription of specific genes. The VDR/1, 25 $(OH)_2$ D complex in the cytoplasm may also interact with transport proteins and other cell proteins in the cytoplasm.

Tissues and Cells that Produce 1, 25 $(OH)_2$ D and/or Carry the VDR[7]

Tissue/Cell	1,25 D	VCR
Endocrine		
Pancreatic β-cells	+	+
Parathyroid	+	+
Parotid	—	+
Thyroid C cells	—	+
Pituitary	—	+
Adrenal	—	+
Musculoskeletal		
Cartilage chondrocytes	+	+
Bone osteoblasts	+	+
Skeletal muscle fibers	—	+
Cardiovascular		
Heart monocytes	+	+
Vascular smooth muscle	—	+
Vascular endothelia	+	+
Gastrointestinal		
Colon mucosal, immune cells	+	+
Esophagus	—	+
Stomach	—	+
Intestine	—	+
Reproductive		
Breast	+	+
Placenta, decidua	+	+
Prostate	+	+
Testis	—	+
Ovary	—	+
Uterus	—	+
Skin		
Keratinocytes	+	+
Hair follicles	—	+
Immune system		
Macrophages/monocytes	+	+
Dendritic cells	+	+
Lymphocytes (activated B, T)	—	+

Physiological Function of Vitamin D

- Calcium Balance
- Cell Differentiation – inhibits cell proliferation and stimulates the differentiation of cells
- Immunity – immune system modulator (the VDR is expressed by most cells of the immune system, including the T cells, antigen presenting cells and macrophages. [10] Macrophages can increase expression the enzyme 25-Hydroxyvitamin D_3-α-hydroxylase gene, which can cause increased conversion of 25 (OH) D to 1,25$(OH)_2$D.[8]
- Insulin Secretion – The pancreatic islet cell are able to produce the enzyme 25-Hydroxyvitamin D_3-α-hydroxylase. It has been postulated that this enzyme may be an important autocrine link between vitamin D status and pancreatic function.
- Blood Pressure Regulation – Biological mechanisms relating vitamin D with hypertension have been proposed for more than 25 years. Vitamin D has been implicated in the proximal regulation of the renin-angiotensin system (RAS) and in interacting with the RAS to determine the intracellular calcium milieu in vascular smooth muscle. [9]

Conditions That May Respond to Vitamin D Therapy[11]

Back pain	Hearing loss
Burns	Influenza
Cancer	Myopathy
Chilblains	Osteomalacia
Colds	Osteoporosis
Congestive Heart Failure	Paget's Disease
Critical Illness	Rickets
Diabetes	Seasonal affective disorder
Fatigue	Tuberculosis
PCOS	

Vitamin D Assessment of Status

Serum 1, 25$(OH)_2$D is not a reliable indicator of vitamin D status due to the fact that a deficiency in vitamin D is compensated for by an increase in PTH, which increases renal produce of this active form of vitamin D. Serum vitamin D_3 (cholecalciferol) is also not a reliable indicator due because its half-life is only about 24 hours.[11] 25(OH) D is considered the most reliable form to assess for vitamin D status. The serum half-life of 25(OH) D is about 3 weeks.

Serum 25(OH) D Reliability:

- There are variation of readings from among different labs
- 25(OH) D is only one of more than 50 vitamin D metabolites that have been identified.[11]
- The body can store vitamin D (cholecalciferol) in the fat tissue, which can be released to be converted to 25(OH)D. this test does not reflect stored vitamin D.
- True vitamin D status as it relates to the regulation of calcium and phosphorous metabolism and to various other biological roles might therefore be a function of complex interactions between different vitamin D metabolites.[11]

[*While very low and very high 25(OH)D levels would seem to be reliable indicators of vitamin D deficiency and excess, respectively, basing clinical decisions on serum 25(OH)D levels between those extremes may not always be appropriate.*[11]

Optimizing Vitamin D Level

A number of studies have shown that supplementing 800 IU/day of vitamin D provides greater benefit than supplementing with 400 IU/day.[11] A safe and effective range to consider is between 800 to 1200 IU/day depending on the person's state of health, BMI, amount of sunlight exposure and skin color. You need to remember that vitamin D is a fat soluble vitamin that can accumulate in the tissues of the body. Prolonged use of high dosage can cause toxic effects. Some of the symptoms of vitamin D toxicity include: fatigue, nausea, polydisia, polyuria, and cardiac arrhythmias.

It appears that the skin may possess mechanisms that regulate the amount of release of vitamin D into circulation. Sunlight exposure to the skin can produce a weak vitamin D agonist that might compete for the VDR binding site thereby modulation vitamin D effects. An interesting side note about the skin is its ability to synthesized corticotrophin-releasing hormone (see abstract below).

Corticotropin releasing Hormone and Proopiomelanocortin Involvement in the Cutaneous Response to Stress

Physiol Rev July 2000 vol. 80 no. 3 979-1020

Abstract

The skin is a known target organ for the proopiomelanocortin (POMC)-derived neuropeptides α-melanocyte stimulating hormone (α-MSH), β-endorphin, and ACTH and also a source of these peptides. Skin expression levels of the POMC gene and POMC/corticotropin releasing hormone (CRH) peptides are not static but are determined by such factors as the physiological changes associated with hair cycle (highest in anagen phase), ultraviolet radiation (UVR) exposure, immune cytokine release, or the presence of cutaneous pathology. Among the cytokines, the proinflammatory interleukin-1 produces important upregulation of cutaneous levels of POMC mRNA, POMC peptides, and MSH receptors; UVR also stimulates expression of all the components of the CRH/POMC system including expression of the corresponding receptors. Molecular characterization of the cutaneous POMC gene shows mRNA forms similar to those found in the pituitary, which are expressed together with shorter variants. The receptors for POMC peptides expressed in the skin are functional and include MC1, MC5 and μ-opiate, although most predominant are those of the MC1 class recognizing MSH and ACTH. Receptors for CRH are also present in the skin. Because expression of, for example, the MC1 receptor is stimulated in a similar dose-dependent manner by UVR, cytokines, MSH peptides or melanin precursors, actions of the ligand peptides represent a stochastic (predictable) nonspecific response to environmental/endogenous stresses. The powerful effects of POMC peptides and probably CRH on the skin pigmentary, immune, and adnexal systems are consistent with stress-neutralizing activity addressed at maintaining skin integrity to restrict disruptions of internal homeostasis. **Hence, cutaneous expression of the CRH/POMC system is highly organized, encoding mediators and receptors similar to the hypothalamic-pituitary-adrenal (HPA) axis. This CRH/POMC skin system appears to generate a function analogous to the HPA axis, that in the skin is expressed as a highly localized response which neutralizes noxious stimuli and attendant immune reactions.**

Vitamin D Deficiency Markers

The Following Markers May Be Seen in Vitamin D Deficiency	
Serum	
25-hydroxyvitamin D	Low
Phosphorus	Low-normal/low
Parathyroid hormone (PTH)	Elevated
Alkaline phosphatase	Elevated
Urinary Markers	
Hydroxyproline, pyridinoline, deoxypyridinoline-N-telopeptide	These are bone collagen by-products that may all be elevated in vitamin D deficiency

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25-Hydroxyvitamin D Recommended Levels in Serum*

***These Recommended Levels May be Changing.** **

25-Hydroxyvitamin D		Indication
nmol/L	ng/mL	
< 75	30	Insufficient
75–250	30–100	Sufficient
> 250	100	Toxic

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***** *The safety and efficacy of giving healthy people large doses of vitamin D (more than 2000 IU/day) for the sole purpose of reaching a target serum 25(OH)D level have not been established. For patients with potentially vitamin D-response diseases and for those who are at risk of developing these diseases, the potential benefits of high-dose vitamin D supplementation should be weighed against the risks.*[11]

American Journal of Clinical Nutrition, Vol. 88, No. 2, 582S-586S, August 2008

Pharmacokinetics of vitamin D toxicity

ABSTRACT

Although researchers first identified the fat-soluble vitamin cholecalciferol almost a century ago and studies have now largely elucidated the transcriptional mechanism of action of its hormonal form, 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$], **we know surprisingly little about mechanisms of vitamin D toxicity.** The lipophilic nature of vitamin D explains its adipose tissue distribution and its slow turnover in the body (half-life ≈2 mo). Its main transported metabolite, 25-hydroxyvitamin D_3 [25$(OH)D_3$], shows a half-life of ≈15 d and circulates at a concentration of 25–200 nmol/L, whereas the hormone 1α,25$(OH)_2D_3$ has a half-life of ≈15 h. Animal experiments involving vitamin D_3 intoxication have established that 25$(OH)D_3$ can reach concentrations up to 2.5 μmol/L, at which it is accompanied by hypercalcemia and other pathological sequelae resulting from a high Ca/PO_4 product. The rise in 25$(OH)D_3$ is accompanied by elevations of its precursor, vitamin D_3, as well as by rises in many of its dihydroxy- metabolites [24,25$(OH)_2D_3$; 25,26$(OH)_2D_3$; and 25$(OH)D_3$-26,23-lactone] but not 1α,25$(OH)_2D_3$. **Early assumptions that 1α,25$(OH)_2D_3$ might cause hypercalcemia in vitamin D toxicity have been replaced by the theories that 25$(OH)D_3$ at pharmacologic concentrations can overcome vitamin D receptor affinity disadvantages to directly stimulate transcription or that total vitamin D metabolite concentrations displace 1α,25$(OH)_2$D from vitamin D binding, increasing its free concentration and thus increasing gene transcription**. Occasional anecdotal reports from humans intoxicated with vitamin D appear to support the latter mechanism. **Although current data support the viewpoint that the biomarker plasma 25(OH)D concentration must rise above 750 nmol/L to produce vitamin D toxicity, the more prudent upper limit of 250 nmol/L might be retained to ensure a wide safety margin.**

Drug Interactions with Vitamin D [11]

- Anticonvulsants – may lead to deficiency
- Anti-tuberculosis drugs (isoniazid and rifampicin) - may lead to deficiency
- Bile salt sequestrants – decreases intestinal absorption leading to deficiency
- Digoxin – caution prescribing excessive dosages of vitamin D (may lead to arrhythmias
- Glucocorticoids – may lower serum levels of 1, 25 $(OH)_2D$ (consider calcium, magnesium and vitamin D supplementation)
- Statins – may lower vitamin D status

Vitamin D and Autoimmunity

Recent attempts to increase vitamin D supplementation to prevent and treat chronic disease have arisen primarily out of observations of low 25(OH) D levels being associated with a variety of diseases. However, new research indicates that these low vitamin D levels are often the result rather than the cause of the disease process, just as in the autoimmune disease, sarcoidosis.[12] Early studies on vitamin D showed promise that various forms of the "vitamin" may be protective against chronic disease, yet systematic reviews and longer-term studies have failed to confirm these findings.[13]

The following is a list of the salient points proposed by Dr. Trevor G. Marshall from the Autoimmune Research Foundation:

- Prevailing theories of vitamin D are imprecise and suggest contradictory understandings of vitamin D metabolism.
- 25-hydroxyvitamin D is immunosuppressive.
- Supplementation of the secosteroid vitamin D temporarily alleviates signs and symptoms of chronic disease but leads to a long-term increase in morbidity.
- Molecular biology suggests that low levels of 25-D are a result rather than a cause of the autoimmune disease process.
- A microbiota of bacterial pathogens may survive in the human body by secreting proteins that antagonize the VDR and disable the innate immune response.
- Elevated levels of 1,25-D exist at the site of disease and are an indication that the innate immune system is responding to an infection.

1,25$(OH)_2$D and Inflammatory Disease [13]

Elevated 1, 25 $(OH)_2$D has been associated with chronic inflammatory and autoimmune disease. The proposed mechanisms are as follows:

- 1, 25$(OH)_2$D is generally well above a healthy range in patients with autoimmune disease due to the inability of cytochrome 24A1 to break down the active metabolite.

- The inability of 1, 25$(OH)_2$D to active VDR in patients with autoimmune illness is supported by data showing that many subjects with autoimmune disease who present with higher than normal levels of 1, 25$(OH)_2$D do not develop hypercalcemia.

- Up-regulation of 1, 25$(OH)_2$D in disease, even without vitamin D supplementation, already interferes with transcription by other receptors. Molecular research shows that excessively high concentrations of 1, 25$(OH)_2$D interfere with numerous hormonal pathways by displacing native ligands from nuclear receptors. Since these receptors also express antimicrobial peptides, when 1, 25$(OH)_2$D reaches unnaturally high levels, the innate immune system's ability to eliminate pathogens is further thwarted.

A study in 2010 concluded that vitamin D may contribute to restoring immune homeostasis in SLE patients through its inhibitory effects on dendritic cells.[14] A study in 2009 conducted at the Cancer Research Center of Hawaii on the association of leptin, 25(OH)D and parathyroid hormone in women concluded that determining the optimal concentrations of micronutrients and/or biomarkers of risk requires consideration of multiple health outcomes and physiological parameters as well as interactions between related molecules.[15] There continues to be much debate and controversy about vitamin D supplementation in patients with autoimmune disease and other chronic diseases. I personal believe that without taking into consideration the patient's history, especially life style and environment, as well as additional primary and functional medicine tests, the debate will continue. As functional medicine practitioners, we know to look beyond the single abnormal lab test finding, and ask our self, why did this happen to this individual and what is the underlying cause?

Proposed Optimal Ranges for 25(OH)D and 1, 25$(OH)_2$ D By FMU[16]

An article in the Journal of Nutrition in January of 2011 recommended to assess both 25(OH)D and 1, 25$(OH)_2$D based on the fact that 1, 25$(OH)_2$D plays a role in cancer, multiple sclerosis, cardiovascular disease and other disease.[17] Therefore, we are adding this analyte to our FMU blood test panel. It is most important that you correlate your 1, 25$(OH)_2$D test results with all other parameters. (Remember that there are no "controls" when prescribing treatment due to biochemical uniqueness of the individual.)

[If there is no improvement in 25(OH)D level after supplementation, consider the following: non-adherence, malabsorption and/or inadequate dosage. If 25(OH)D is optimal or high and 1, $25(OH)_2D$ is low, consider renal disease]

Analyte		
25(OH) D	30 – 40 ng/ml	70 – 100 nmol/L
1, $25(OH)_2D$	17 – 53 pg/ml	48 – 108 pmol/L

In nutritional rickets and osteomalacia:

- 25(OH)D is very low
- 1, 25 $(OH)_2D$ is undetectable
- Low serum phosphorus
- High alkaline phosphatase
- Serum calcium low to normal
- Serum PTH increased
- Urinary calcium low

Serum 1, 25 $(OH)_2D$ is variable at best. Always correlate lab value with the patient history and other lab tests.

Summary

The rapidly ever changing field of functional medicine can be challenging to the practitioner with regard to treatment recommendations. You just learned another example of the potential negative effects of excessive supplementation with vitamin D. You also learned that a low 25(OH) vitamin D and high 1, 25 $(OH)_2D$ can be a sign of chronic inflammation. Functional Medicine University's position on lab testing is to order both 25(OH) vitamin D and 1, 25 $(OH)_2$ vitamin D on any patient with suspected chronic inflammation and/or autoimmune disease.

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