Vitamin D Deficiency (Hypovitaminosis D) and Osteomalacia — Symptoms and Treatment

Vitamin D is a fat-soluble substance vitamin. This vitamin is essential for proper function of the human body and is considered a hormone rather than a vitamin. Its synthesis takes place in the body - under ideal conditions, it may not be required in our diet. In bone tissue, where vitamin D is required the most, it is needed for deposition of calcium in bone and its lack usually leads to various pathologies including rickets in children and osteomalacia in adults. To understand the pathology of these diseases, we must first learn how this vitamin is produced and the effects it has on various systems in the human body.

Production and Effects of Vitamin D
Source of vitamin D

7-Dehydrocholecalciferol, a substance normally found in skin, is broken down by UV radiation from the sun to form cholecalciferol (vitamin D3). Cholecalciferol can also be ingested in various food compounds such as egg yolk, cod liver oil and beef liver. The cholecalciferol is then converted to 25-hydroxycholecalciferol in the liver. Vitamin D 25-hydroxylase is a member of the cytochrome P450 superfamily of enzymes.

The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Found in the liver, this enzyme is a microsomal vitamin D hydroxylase that converts vitamin D into 25-hydroxyvitamin D (calcidiol), which is the major circulatory form of the vitamin. It should be noted that this process has a negative feedback mechanism that regulates the levels of 25-hydroxycholecalciferol in plasma.

Activation of vitamin D

25-hydroxycholecalciferol moves to the proximal tubules of the kidney where it is hydroxylated to 1,25 dihydroxycholecalciferol by the action of α1-hydroxylase. This is the most active form of vitamin D. It is to be noted that this process also requires parathyroid hormone. Without this hormone, 1,25 dihydroxycholecalciferol will not be formed. It is thus of paramount importance that this hormone is present.

Calcium levels above 10mg/100ml suppress the secretion of parathyroid hormone. Below this level, parathyroid hormone helps in the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. But levels of calcium above this suppress parathyroid hormone production and hinder production of 1,25-
dihydrocholecalciferol. Instead, another compound with no vitamin D effect, known as 24,25 dihydrocholecalciferol is formed. High levels of plasma calcium thus impair the formation of 1,25- dihydroxycholecalciferol.

**Function of vitamin D**

The active form of vitamin D has various effects on different systems including the renal system, skeletal system and the gastro-intestinal system and regulates absorption as well as excretion of calcium and phosphate.

**Gastrointestinal tract**

Calcium is absorbed in the small intestine by two general mechanisms: a transcellular active transport process, located largely in the duodenum and upper jejunum; and a paracellular, passive process mediated by facilitated diffusion that functions throughout the length of the intestine.

The transcellular process involves three major steps: entry across the brush border through a molecular structure termed CaT1, intracellular diffusion, mediated largely by the cytosolic calcium-binding protein (calbindinD or CaBP); and extrusion, mediated largely by the CaATPase. Chyme travels down the intestinal lumen in approximately 3 h, spending only minutes in the duodenum, but over 2 h in the distal half of the small intestine.

When calcium intake is low, transcellular calcium transport accounts for a substantial fraction of the absorbed calcium. When calcium intake is high, transcellular active transport accounts for only a minor portion of the absorbed calcium, because of the short sojourn time and because CaT1 and CaBP, both rate-limiting, are downregulated when calcium intake is high. Biosynthesis of CaBP is fully and CaT1 function is approximately 90% vitamin D-dependent. Phosphate absorption in the intestines is also enhanced by vitamin D.
**Kidney**

In the kidneys **Vit D promotes absorption of both calcium and phosphate** by the epithelial cells of the renal tubules. This is **unlike the effects of parathyroid hormone** on the kidney which promotes absorption of calcium but promotes phosphate excretion. We shall later see the effects of the hormone on bone in developing diseases such as rickets.

**Bones**

In bone, vitamin D in high quantities causes resorption of bone. Without it, the effect of parathyroid hormone on bone resorption is significantly reduced. Thus it helps in the cumulative effect of the parathyroid hormone. In small amounts, **Vit D enhances bone mineralization**. Thus, in small quantities it enhances the deposition of calcium and phosphate on the bone.

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**Differential Analysis of Vitamin D Dysfunction and Deficiency**

The differential diagnosis involves:

**Dietary lack of the vitamin D**

This is especially important in the setting of developing countries, where the fortified source of vitamin D in the food is unavailable for consumption.
Lack of the exposure to sunlight

It is also plausible that the geographical location of the place away from the equator and with excessive exposure to winter (given that the exposure to sunlight decreases to a considerable extent) predisposes to the development of deficiency of vitamin D. Concurrently, the elderly have a reduction in the synthesis of vitamin D in the skin and other problems such as achlorhydria which decreases the absorption of vitamin D.

Drug-induced

- In women who were treated for osteoporosis and on the therapy like bisphosphonates such as raloxifene and calcitonin, there occurs a risk of vitamin D deficiency
- On any enzyme inducers such as phenobarbital and phenytoin. These drugs basically increase the metabolism of vitamin D.

Malabsorptive states

Vitamin D being a fat soluble vitamin is affected in the malabsorptive states, which also results in the disruption of enterohepatic circulation. Malabsorptive states are for example:

- **Cystic fibrosis**
- The bariatric surgery and gastrectomy are some of the other reason which predisposes to the vitamin D deficiency.
- Reduction in the absorptive area of the intestine following the removal and resection of the segment of the bowel (small bowel syndrome), celiac sprue.

Chronic renal disease

This is because the activation of 25 hydroxyvitamin D to 1,25 dihydroxyvitamin also known as calcitriol occurs in the kidney. This is important for the function of vitamin D.

Nephrotic syndrome

In patients with nephrotic syndrome, due to the excretion of vitamin D binding proteins (25 hydroxyvitamin D is bounded to this protein in the serum) there occurs decrease in the concentration of 25 hydroxyvitamin D in the serum.
Advanced end stage liver disease

Extensive skin burn, which prevents the synthesis of the vitamin D

Nonspecific musculoskeletal pain. Patients with this disorder have vitamin D deficiency

Increase and descent of Vitamin D:

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<tr>
<th></th>
<th>Vitamin D deficiency</th>
<th>Vitamin D end-organ resistance</th>
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<tr>
<td>Vitamin D\textsubscript{plasma}</td>
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<tr>
<td>Plasma Ca\textsuperscript{2+}</td>
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<tr>
<td>Urine Ca\textsuperscript{2+}</td>
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<td>Plasma PO\textsubscript{4\textsuperscript{2-}}</td>
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<td>Urine PO\textsubscript{4\textsuperscript{2-}}</td>
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Disorders Related to Vitamin D Deficiency

Rickets and osteomalacia

Rickets and osteomalacia have been explained in great detail in a separate article and the readers are encouraged to have a read that article to enhance their knowledge on the topic. Both the occurrence of vitamin D dependent type 1 rickets and vitamin D resistant rickets have been discussed. Osteomalacia is the adult counterpart of rickets.

Interpretation of Serum Calcium and Phosphate

The normal range of calcium is 8.8 to 10.3 mg/dl (2.2-4.6 mmol/L). Calcium is present in 3 forms in the body. Either it is bound to organic and inorganic anions like citrate (which constitutes 15 %) or it is bound to albumin (which constitutes 40 %) or it exists in the free active ionized form.

Though total calcium consists of both bound and free-form, in diseases such as hypoalbuminemia, there is a disproportionate decline of the bound calcium. It should also be noted that for the establishment of the diagnosis, the concomitant measurement of the parathyroid hormone and also of vitamin D is recommended.

In acute respiratory alkalosis, the increase in the binding of calcium to albumin (due to the change in the extracellular pH) causes a decrease in the ionized calcium level.

In multiple myeloma, there is an increase in the total calcium in the body (due to the binding of calcium to the protein), increase in the free calcium level (due to the activation of the osteolytic activity leading) and elevation of the phosphate level.

In the deficiency state of vitamin D, the level of calcium may be corrected by the compensatory secretion of parathyroid hormone.

Simplified Calcium/Phosphate Interpretation:

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<thead>
<tr>
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<th>Serum calcium</th>
<th>Serum phosphate</th>
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<tbody>
<tr>
<td>Low Vitamin D action</td>
<td>↓</td>
<td>↓ unless renal failure</td>
</tr>
<tr>
<td>High Vitamin D action</td>
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Low PTH action

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<th>Low PTH action</th>
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</thead>
<tbody>
<tr>
<td>High PTH (or PTHrP)</td>
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<td>↓ unless renal failure</td>
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**Bottom line:** Calcium and phosphate tend to deviate together (both up or both down) in Vitamin D derangements, whereas they deviate in opposite directions in parathyroid disease.

In patients with [chronic kidney disease](https://www.cdc.gov/dialysis/diagnosis/chronic_kidney_disease.html), it is preferable to measure ionized serum calcium. This is because estimation of ionized serum calcium from total serum calcium is unreliable due to the accompanying acidosis and also overestimated correction of the amount of calcium bound to serum albumin.

In case of the [osteomalacia](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC17739/) scenario will be a decrease in serum vitamin D, decrease in serum and urinary calcium, decrease in the phosphate level, along with the compensatory elevation of PTH and elevation of bone-derived alkaline phosphatase.

In [rickets](https://www.uptodate.com/contents/rickets), there is also a decrease in the serum calcium and serum phosphate along with an increase in bone-derived alkaline phosphatase. Vitamin D levels vary depending on the type of rickets. In vitamin D sensitive rickets, there is a decrease in vitamin D levels but in vitamin D resistant rickets there is a normal level of the hormone vitamin D.

It should be noted that in [hypocalcemia](https://www.cdc.gov/dialysis/diagnosis/hypocalcemia.html) which occurs following vitamin D deficiency, the concomitant increase in the parathyroid hormone level, which occurs as a compensatory mechanism, masks the development of hypocalcemia and at the same time increases the urinary phosphate excretion leading to the development of [hypophosphatemia](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6856025/). The circulating [25 hydroxyvitamin D](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474105/) also known as [calcidiol](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474105/) is the best index for the sufficiency of vitamin D in the body.

**Hypercalcemia**

Hypercalcemia is an increase in the calcium level greater than 10.5 to 11 mg/dl. Measurement of serum calcium and phosphorus, along with renal function should be considered. Parathyroid hormone levels should also be measured.

If parathormone is normal, then the diagnosis of [familial benign hypercalcemia](https://www.cdc.gov/dialysis/diagnosis/familial_benign_hypercalcemia.html) is considered. With the elevation of parathormone, primary [hyperparathyroidism](https://www.cdc.gov/dialysis/diagnosis/hyperparathyroidism.html) or tertiary hyperparathyroidism should be considered. For primary hyperparathyroidism, [medical treatment](https://www.cdc.gov/dialysis/diagnosis/medical_treatment.html) is considered. If the patient is symptomatic and in case of tertiary hyperparathyroidism, [surgery](https://www.cdc.gov/dialysis/diagnosis/surgery.html) is the treatment.

**References**


[Clinical manifestations, diagnosis, and treatment of osteomalacia](https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-treatment-of-osteomalacia) via uptodate.com


[Rickets](https://www.medscape.com/viewarticle/773536) via medscape.com
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