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

See online here

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. Cholecalciferol is then converted to \textbf{25-hydroxycholecalciferol} in the liver by vitamin D 25-hydroxylase. Vitamin D 25-hydroxylase is a member of the cytochrome P450 superfamily of enzymes.

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

\textbf{Activation of vitamin D}

25-hydroxycholecalciferol moves to the \textbf{proximal tubules of the kidney} where it is hydroxylated by \textit{α1-hydroxylase} to \textbf{1,25 dihydroxycholecalciferol}, which is the most active form of vitamin D. This process also requires \textbf{the parathyroid hormone} because without this hormone 1,25 dihydroxycholecalciferol will not be formed. Calcium levels above 10 mg/100 mL suppress the secretion of parathyroid hormone. Below this level, the parathyroid hormone helps in the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. However, calcium levels above this suppress parathyroid hormone production and hinder the production of 1,25-dihydroxycholecalciferol. Instead, another compound with no vitamin D effect, known as \textbf{24,25-dihydroxycholecalciferol} is formed. High plasma levels of calcium thus impair the formation of 1,25-dihydroxycholecalciferol.
Functions of vitamin D

The active form of vitamin D has various effects on different systems, including the renal, skeletal, and gastrointestinal systems, and it regulates the absorption and excretion of calcium and phosphate.

Gastrointestinal tract

Calcium is absorbed in the small intestine by 2 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 3 major steps: entry across the brush border through a molecular structure termed CaT1; intracellular diffusion, mediated largely by the cytosolic calcium-binding protein (calbindin D or CaBP); and extrusion, mediated largely by CaATPase. Chyme travels down the intestinal lumen in approx. 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 transit time and because CaT1 and CaBP, which are both rate-limiting, are downregulated when calcium intake is high. Biosynthesis of CaBP is fully vitamin D-dependent, while the CaT1 function is about 90% vitamin D-dependent. Phosphate absorption in the intestines is also enhanced by vitamin D.

Kidney

In the kidneys, vitamin D promotes the 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 calcium absorption and phosphate excretion. The effects of the hormone on bone in the development of diseases such as rickets are discussed later.
Bones

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

Differential Analysis of Vitamin D Dysfunction and Deficiency

The differential diagnosis includes:

**Dietary lack of vitamin D**

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

It is also plausible that geographical locations away from the equator and the winter season (given that exposure to sunlight is decreased considerably) predispose to vitamin D deficiency. The elderly also have a reduction in the synthesis of vitamin D in the skin and other problems such as achlorhydria which decrease the absorption of vitamin D.

Drug-induced

- In women being treated for osteoporosis and in those receiving drugs like bisphosphonates (such as raloxifene) and calcitonin, there is a risk of vitamin D deficiency
- Enzyme inducers such as phenobarbital and phenytoin basically increase the metabolism of vitamin D.

Malabsorptive states

Vitamin D is a fat-soluble vitamin and it is affected by malabsorptive states, which also result in the disruption of enterohepatic circulation. Malabsorptive states include:

- Cystic fibrosis
- Bariatric surgery and gastrectomy are some other conditions that predispose to vitamin D deficiency
- Reduction in the absorptive area of the intestine following the removal and resection of the bowel segment (small bowel syndrome), and celiac sprue

Chronic renal disease

The activation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol) occurs in the kidney. This is important for the function of vitamin D. Thus, chronic renal failure negatively impacts this activation process.

Nephrotic syndrome

In patients with nephrotic syndrome, because of the excretion of vitamin D-binding proteins (25-hydroxyvitamin D is bound to this protein in the serum), a decrease in the concentration of 25-hydroxyvitamin D occurs in the serum.

Advanced end-stage liver disease

Extensive skin burn, which prevents the synthesis of vitamin D

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

Increase and decrease of vitamin D:

<table>
<thead>
<tr>
<th>Vitamin D deficiency</th>
<th>Vitamin D end-organ resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D_{plasma}</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma Ca^{2+}</td>
<td>↓</td>
</tr>
<tr>
<td>Urine Ca^{2+}</td>
<td>↑</td>
</tr>
<tr>
<td>Plasma PO_{4}^{2-}</td>
<td>↓</td>
</tr>
<tr>
<td>Urine PO_{4}^{2-}</td>
<td>↑</td>
</tr>
</tbody>
</table>
Disorders Related to Vitamin D Deficiency

Rickets and osteomalacia

Rickets and osteomalacia have been explained in great detail in a separate article and readers are encouraged to review 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 8.8–10.3 mg/dL (2.2–4.6 mmol/L). Calcium is present in 3 forms in the body. It is either bound to organic and inorganic anions like citrate (occurrence 15%) or bound to albumin (occurrence 40%); it can also exist in the free active ionized form.

Although total calcium consists of both bound and free forms, in diseases such as hypoalbuminemia, there is a disproportionate decline of bound calcium. It should also be noted that to establish a diagnosis, the concomitant measurement of parathyroid hormone levels and vitamin D is recommended.

In acute respiratory alkalosis, the increased binding of calcium to albumin (due to changes in extracellular pH) causes a decrease in ionized calcium levels.

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

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

Simplified Calcium/Phosphate Interpretation:

<table>
<thead>
<tr>
<th></th>
<th>Serum calcium</th>
<th>Serum phosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low vitamin D action</td>
<td>↓</td>
<td>↓ unless renal failure</td>
</tr>
<tr>
<td>High vitamin D action</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Low PTH action</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>High PTH (or PTHrP)</td>
<td>↑</td>
<td>↓ unless renal failure</td>
</tr>
</tbody>
</table>

Note: 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, it is preferable to measure ionized serum calcium. This is because the estimation of ionized serum calcium from total serum calcium is unreliable because of the accompanying acidosis, and also because of the overestimated correction of the amount of calcium bound to serum albumin.

In the case of osteomalacia, the scenario will be reductions in serum vitamin D, serum and urinary calcium, and phosphate level, along with compensatory elevations of parathyroid hormone and bone-derived alkaline phosphatase.

In rickets, there is also a decrease in 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, the level of vitamin D is normal.
It should be noted that in hypocalcemia, which occurs following vitamin D deficiency, the concomitant increase in parathyroid hormone levels, which occurs as a compensatory mechanism, masks the development of hypocalcemia. At the same time, this increase in parathyroid hormone levels results in increased urinary phosphate excretion, leading to the development of hypophosphatemia. Circulating 25-hydroxyvitamin D is the best index of vitamin D sufficiency in the body.

**Hypercalcemia**

Hypercalcemia is an increase in calcium levels above 10.5 mg/dL. Measurement of serum calcium and phosphorus, along with the assessment of renal function should be considered. Parathyroid hormone levels should also be measured.

If parathyroid hormone levels are normal, then a diagnosis of familial benign hypercalcemia is suggested. With the elevation of parathyroid hormone, primary hyperparathyroidism or tertiary hyperparathyroidism should be considered. For primary hyperparathyroidism, medical treatment is considered. If the patient is symptomatic and in the case of tertiary hyperparathyroidism, surgery is the treatment of choice.

**References**


Clinical manifestations, diagnosis, and treatment of osteomalacia via uptodate.com


Rickets via medscape.com

**Legal Note:** Unless otherwise stated, all rights reserved by Lecturio GmbH. For further legal regulations see our legal information page.