EDUCATIONAL COMMENTARY – VITAMIN D

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LEARNING OUTCOMES

On completion of this exercise, the participant should be able to

- explain the synthesis and metabolism of vitamin D.
- describe diseases and conditions associated with vitamin D deficiency and insufficiency.
- identify methods available to measure serum 25-hydroxyvitamin D concentrations.
- interpret serum 25-hydroxyvitamin D concentration as an indicator of vitamin D status.

Introduction

In the past five years, laboratories have experienced a dramatic increase in test requests for vitamin D levels. The reason for this increase can be attributed to a combination of epidemiologic studies, clinical trials, and publications that indicate relatively high rates of vitamin D deficiency, insufficiency, or both in the general population, and to correlations of such deficiency with increased risk for many conditions and diseases.

Vitamin D and Metabolites

Vitamin D exists in two forms. D<sub>2</sub>, ergocalciferol, is the dietary form, found in fish, plants, and fungus. D<sub>3</sub>, cholecalciferol, is mostly produced by photosynthesis in the skin from exposure to sunlight, but is also found in dietary animal products. Both forms of vitamin D are metabolized to more active dihydroxy forms (1,25-(OH)<sub>2</sub>D). The first step of the metabolic process occurs in the liver, producing 25-hydroxyvitamin D, and the second step occurs in the kidneys. Vitamin D functions more like a prohormone than a vitamin; the active form, 1,25-(OH)<sub>2</sub>D, has hormonal functions. 1,25-Dihydroxyvitamin D promotes increased blood calcium and phosphorus by increasing intestinal calcium and phosphate absorption and renal reabsorption of both. It also facilitates the action of parathyroid hormone (PTH) on osteoblasts, thereby increasing mineralization during bone formation. For decades, vitamin D was considered to function solely in bone mineralization and calcium utilization. It is now known that the vitamin D receptor is found in more than 36 cell types and that 10 organs in addition to the kidneys can produce the active hormone 1,25-(OH)<sub>2</sub>D. The exact role of 1,25-(OH)<sub>2</sub>D in these cells and organs is yet to be elucidated, but correlation of deficiency with disease processes indicates that the hormone is involved with essential functions.
Deficiency and Insufficiency

The cutaneous synthesis of vitamin D is affected by factors that include geography, seasonal exposure, skin color, age, time of exposure to sunlight, cloud cover, use of sunscreen, and body mass index (calculated as weight in kilograms divided by height in meters squared). People living at latitudes above 33° north, the approximate location of Atlanta, Georgia, are at higher risk for vitamin D deficiency and insufficiency, particularly during winter months. The presence of the skin pigment melanin in darker-skinned people reduces synthesis of vitamin D. Use of sunscreen or wearing clothes that minimize skin exposure also reduces synthesis. The inverse correlation of chronological age and vitamin D levels may be caused by decreased renal function. Vitamin D is fat soluble and sequestration in adipose tissue may be responsible for the higher risk for deficiency or insufficiency associated with increasing body mass index. In addition to decreased cutaneous production of vitamin D, other causes of deficiency or insufficiency include inadequate dietary vitamin D and liver or kidney disease.

The relationship of vitamin D to bone metabolism has been known for years. Vitamin D deficiency causes rickets, the childhood disease characterized by softening and weakening of bone. The introduction of vitamin D–fortified milk in the 1930’s tremendously decreased the incidence of rickets. In adults, vitamin D deficiency is one of the causes of type two osteoporosis. Studies have also linked vitamin D deficiency to many other conditions, including hypertension; obesity; diabetes; cardiovascular disease; multiple sclerosis; cancers of the colon, breast, prostate, and pancreas; autism; systemic lupus erythematosus and other autoimmune diseases; as well as to all-cause mortality. These conditions account for more than 60% of deaths in the Western world.

Laboratory Testing

Although the dihydroxy form is the biologically active metabolite of vitamin D, concentrations of 1,25-(OH)2D typically remain within or even above reference intervals in patients with vitamin D deficiency or insufficiency. To assess vitamin D stores, it is necessary to measure levels of serum 25-hydroxyvitamin D (25-OH vitamin D), not the dihydroxy form. The 1,25-(OH)2D assay, however, is of value for the differential diagnosis of hypercalcemic syndromes and inborn and acquired disorders of 25-OH vitamin D metabolism.

Methods for measuring these compounds include chemiluminescent, enzyme, and radio immunoassays and high-performance liquid chromatography and liquid chromatography tandem mass spectrometry. The immunoassay methods measure the total 25-OH vitamin D (D2 and D3) based on antibody cross-reactivity, whereas the chromatographic methods measure the D2 and D3 forms separately.

Defining Reference Levels

Because establishment of reference ranges for 25-OH vitamin D determines the definition of both deficiency and insufficiency, there is an ongoing debate over the appropriate cutoffs for the reference range. The lower limit of the range determines the level of vitamin D adequacy; levels below this value define vitamin D insufficiency and deficiency. One method used to determine the lower limit is a healthy-population study using PTH levels as a
surrogate marker for vitamin D deficiency. Elevated PTH levels are seen in vitamin D deficiency, and these levels decrease as the 25-OH vitamin D level increases. The lower limit of the reference range is the 25-OH vitamin D level at which PTH concentrations plateau. Another way to establish the reference range is to use the range determined from a healthy-population study of highly sun-exposed individuals. Although there are some differences in ranges, there is agreement that levels of 25-OH vitamin D less than 20 ng/mL indicate deficiency. Levels between 21 and 29 ng/mL are usually defined as indicating vitamin D insufficiency, but some laboratories use 20 ng/mL as the lower limit of the reference range. Using these levels, an estimated one billion people worldwide are considered deficient or insufficient in vitamin D. In 2010, the Institute of Medicine (IOM) assessed data associated with calcium and vitamin D and issued a 1116-page report which adopted a reference range for vitamin D adequacy of 20-50 ng/mL and defined deficiency as less than 12 ng/mL and inadequacy as 12-19 ng/mL (Table). Using these levels, the National Center for Health Statistics reported that in 2001 through 2006, two-thirds of persons aged one year and older in the United States had serum 25-OH vitamin D levels considered sufficient.

Table. Institute of Medicine Categories of Vitamin D Status Based on Serum 25-Hydroxyvitamin D Concentrations*

<table>
<thead>
<tr>
<th>Vitamin D Status</th>
<th>25-Hydroxyvitamin D Level</th>
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<tbody>
<tr>
<td>Sufficient</td>
<td>20-50 ng/mL (50-125 nmol/L)</td>
</tr>
<tr>
<td>At risk for deficiency</td>
<td>&lt;12 ng/mL (&lt;30 nmol/L)</td>
</tr>
<tr>
<td>At risk for inadequacy</td>
<td>12-19 ng/mL (30-49 nmol/L)</td>
</tr>
<tr>
<td>Possibly harmful</td>
<td>&gt;50 ng/mL (&gt;125 nmol/L)</td>
</tr>
</tbody>
</table>

*Sources: Institute of Medicine and National Center for Health Statistics

The appropriate upper limit of the 25-OH vitamin D reference range is debated. Laboratories currently use upper limits from 50 ng/mL to as high as 80 ng/mL. There have been recommendations to raise this to as high as 150 ng/mL because of reports of individuals in sunlight-rich regions with levels up to 100 ng/mL with no toxic effects. The IOM review committee concluded that levels greater than 50 ng/mL should be considered possibly harmful.

Treatment and Prevention of Vitamin D Deficiency or Insufficiency

Recommendations for treatment of vitamin D deficiency (<20 ng/mL) include treatment with 50,000 units of vitamin D2 orally once per week for six to eight weeks and 800 to 1000 IU daily thereafter. Patients with liver disease should receive 25-hydroxyvitamin D supplementation, and patients with renal failure should receive 1,25-dihydroxyvitamin D supplementation. The IOM report raised the recommended dietary allowance (RDA) for all individuals older than one year through adulthood to 600 IU/day and added that people aged 71 and older may need as much as 800 IU/day. The IOM report did not include RDA recommendations for infants younger than one year, but in 2008, the American Academy of Pediatrics recommended that all children receive 400 IU/day of
either D₂ or D₃ beginning in the first few days of life. Some experts and professional organizations have recommended that the adult RDA be raised to as high as 2000 IU/day; others have recommended intake levels between 2000 and 4000 IU/day in order to reduce risks for certain types of cancer and autoimmune disease. The IOM committee concluded that risk for harm begins to increase once intake of vitamin D exceeds 4000 IU/day. Although it rarely occurs, excessive ingestion of vitamin D can cause toxicity.

References


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