VITAMIN D:
AN OVERVIEW

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ABSTRACT
Vitamin D deficiency is recognized to be a worldwide pandemic, which has been associated with increased risk of common cancers, autoimmune disorders, cardiovascular and other diseases. Low levels of vitamin D are associated with a worsening of these diseases once they have developed; and, there are well-defined mechanisms that could explain these associations. Currently, there is a lack of medical consensus on a standard prevention protocol for vitamin D supplementation. To benefit health, vitamin D must circulate at accepted serum levels. When an individual has inadequate sun exposure vitamin D is needed to achieve optimal blood levels. All age groups can suffer from vitamin D deficiency.
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Policy Statement
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Continuing Education Credit Designation
This educational activity is credited for 2 hours. Nurses may only claim credit commensurate with the credit awarded for completion of this course activity. Pharmacology content is 1 hour.

Statement of Learning Need
Nursing knowledge of the physiological functions of vitamin D and the systemic effects of vitamin D deficiency will help them educate patients on the prevention and treatment of vitamin D deficiency. Patients treated for vitamin D deficiency should be aware of the signs of acute and chronic vitamin D intoxication.

Course Purpose
This course will help nurses identify signs and symptoms of vitamin D deficiency and its treatment.
Target Audience
Advanced Practice Registered Nurses and Registered Nurses
(Interdisciplinary Health Team Members, including Vocational Nurses and Medical Assistants may obtain a Certificate of Completion)

Course Author & Planning Team Conflict of Interest Disclosures
Dana Bartlett, RN, BSN, MSN, MA, William S. Cook, PhD, Douglas Lawrence, MA, Susan DePasquale, MSN, FPMHNP-BC – all have no disclosures

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Please take time to complete a self-assessment of knowledge, on page 4, sample questions before reading the article.

Opportunity to complete a self-assessment of knowledge learned will be provided at the end of the course.
1. One of the primary functions of vitamin D is:
   a. control of muscle contraction
   b. control of calcium and phosphorus metabolism
   c. control of potassium and sodium metabolism
   d. control of renal blood flow

2. Good dietary sources of vitamin D are:
   a. whole grains and fruits
   b. leafy green vegetables and red meat
   c. fortified milk and certain fishes
   d. citrus fruits and nuts

3. True or false: Infants who are exclusively breast-fed are at risk for vitamin D deficiency.
   a. True
   b. False

4. Which of these drugs may influence vitamin D levels?
   a. Statins, anti-epileptic drugs
   b. Beta-blockers, opioid analgesics
   c. ACE inhibitors, glucocorticoids
   d. Calcium channel blockers, non-steroidal anti-inflammatories

5. Vitamin D intoxication is primarily characterized by:
   a. hyperkalemia
   b. hypercalcemia
   c. hypernatremia
   d. hypermagnesemia
Introduction

Vitamin D and the deficiency of vitamin D have been the focus of much attention from the medical and scientific communities in the past decade. Vitamin D deficiency has been described as a pandemic. This course discusses the following key aspects:

- The synthesis and metabolism of vitamin D
- The physiological functions of vitamin D
- Vitamin D deficiency - how it happens and how it is diagnosed
- The systemic effects of vitamin D deficiency
- Treatment of vitamin D deficiency
- The interaction between medications and vitamin D
- Acute and chronic vitamin D intoxication

Although it is true that millions of people in the United States and in the world have low levels of vitamin D, to describe vitamin D deficiency as a pandemic may not, in one sense, be completely accurate. Doing so implies that there are adverse health risks from this phenomenon; however, aside from the well-known effects of vitamin D deficiency on bone health, the scientific evidence is inconclusive that a low level of vitamin D causes diseases or affects any other organ system. There are strong and well-established associations between vitamin D deficiency and an increased risk of developing autoimmune, cardiovascular, neurological and many other pathologies. Low levels of vitamin D are associated with a worsening of these diseases once they have developed. And there are well-defined mechanisms that could explain these associations.

When the data is examined closely, the final link, a definite cause and effect, for disease states due to vitamin D deficiency has not yet been found. Some people who have low levels of vitamin D do not get cancer, heart disease, or multiple sclerosis. Supplementation does not seem to prevent disease or act as an effective therapy. Additionally, the mechanisms by which researchers have
explained the association between vitamin D deficiency and disease have at times only been studied in cell cultures or in animals. Much has been discovered about vitamin D and its possible role in health and preventative medicine. However, at this point, the questions are more numerous than answers.

**Vitamin D: Overview**

Vitamin D is a fat-soluble vitamin that is needed for control of calcium and phosphorous metabolism, normal immune function, modulation of cell growth, and several other body processes. Vitamin D can be obtained by dietary intake of foods such as the flesh of certain fatty fishes, fish oils, vitamin D fortified milk, and (to a small degree) egg yolks, some mushrooms, beef liver, and cheese. Vitamin D is also synthesized in the skin by exposure of the skin to ultraviolet B (UVB) radiation from sunlight.

Vitamin D is synthesized by the skin or ingested as cholecalciferol, or D$_3$, and cholecalciferol is a pro-vitamin. In order for vitamin D in the form of cholecalciferol and ergocalciferol (ergocalciferol will be discussed in the next paragraph) to be biologically active it must be first hydroxylated in the liver to become to 25-hydroxyvitamin D, a.k.a 25(OH) D or calcidiol, the major circulating form of vitamin D. Calcidiol is then hydroxylated by the kidneys to 1,25-dihydroxyvitamin D, or calcitriol, the metabolically active form of vitamin D.$^{1,2}$ Tissues and organs have vitamin D receptors, and the physiological actions of vitamin D are mediated by the binding of vitamin D with these receptors.

There is another form of vitamin D: *ergocalciferol*, which is also known as vitamin D$_2$. Ergocalciferol is found in some plants and fungi, but human consumption is almost exclusively in the form of D$_2$ supplements that are produced by the irradiation of yeast. Cholecalciferol and ergocalciferol are essentially identical compounds and they were long considered to be equivalent to use for patients
who needed supplemental vitamin D. However, there is evidence that this may not be true, and this issue will be discussed briefly later in this learning module.

Vitamin D is absorbed in the small bowel (jejunum), and dietary fat and bile are needed for vitamin D to be absorbed; hence, the term fat-soluble vitamin. Excess vitamin D that is not needed immediately is stored in the liver and in fat tissues.

**Learning Break:** A vitamin is defined as an essential nutrient that cannot be synthesized by the body; therefore, vitamin D is not truly a vitamin. Vitamin D is a hormone. However, the use of the term vitamin D is so common and so well understood that it is used almost exclusively.

The Physiological Functions Of Vitamin D

The section below will provide some basic information about the benefits of vitamin D as well as the systemic effects when there is a long-term deficit as observed in population-based and animal studies.

**Calcium and Phosphorus Metabolism**

A normal serum calcium level is important for blood clotting, bone growth and density, and optimal functioning of the cardiac and nervous systems. Normal serum phosphorus levels are essential for adequate mineralization of the bones. Calcium and phosphorus metabolism and absorption are regulated in large part by vitamin D, and low serum vitamin D levels can cause hypocalcemia and hypophosphatemia.
The parathyroid gland, in response to low serum calcium levels, will secrete parathyroid hormone. Parathyroid hormone increases the activity of 25-hydroxyvitamin D₃ 1-hydroxylase, an enzyme in the kidney that stimulates the production of 1,25-dihydroxyvitamin D, calcitrol. Calcitrol increases the serum calcium level according to the following pathways and processes:

1) Increasing the level of a transport system in the small bowel that increases the absorption of calcium by the gut
2) Increasing the amount of calcium that is reabsorbed by the kidneys
3) Mobilizing calcium from the bone into the serum

**Immune System**

Animal studies and some supplementation studies done with humans have shown that vitamin D increases the activity of the immune system, decreases the inflammatory response, and inhibits the development of autoimmunity.

**Insulin Secretion and Insulin Sensitivity**

Low levels of vitamin D₃ have been reported to be associated with decreased insulin production and increased insulin sensitivity in people with type 2 diabetes. There is also epidemiological evidence suggesting that low levels of vitamin D are a risk factor for the development of type 2 diabetes.

**Renin-Angiotensin System**

Animal studies indicate that vitamin D deficiency affects the function of the renin-angiotensin system, causing hypertension and cardiac hypertrophy. Observational studies in humans have found an association between low serum levels of vitamin D and an increased incidence of hypertension.

**Cell Differentiation and Proliferation**

Vitamin D is involved in the control of cell differentiation and the inhibition of cell proliferation. There are cell-specific factors that influence cell responsiveness to
vitamin D related to cell growth and differentiation, which is outside the scope of this study.

**Vitamin D: Sources And Daily Requirements**

There are few foods that are good sources of vitamin D content: most of the nutritional intake of vitamin D is from fortified foods. The following table is from the National Institutes of Health website.

**Food Sources of Vitamin D**

<table>
<thead>
<tr>
<th>Food</th>
<th>IUs per serving*</th>
<th>Percent DV**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil, 1 tablespoon</td>
<td>1,360</td>
<td>340</td>
</tr>
<tr>
<td>Swordfish, cooked, 3 ounces</td>
<td>566</td>
<td>142</td>
</tr>
<tr>
<td>Salmon (sockeye), cooked, 3 ounces</td>
<td>447</td>
<td>112</td>
</tr>
<tr>
<td>Tuna fish, canned in water, drained, 3 ounces</td>
<td>154</td>
<td>39</td>
</tr>
<tr>
<td>Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)</td>
<td>137</td>
<td>34</td>
</tr>
<tr>
<td>Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup</td>
<td>115-124</td>
<td>29-31</td>
</tr>
<tr>
<td>Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Margarine, fortified, 1 tablespoon</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>Sardines, canned in oil, drained, 2 sardines</td>
<td>46</td>
<td>12</td>
</tr>
<tr>
<td>Liver, beef, cooked, 3 ounces</td>
<td>42</td>
<td>11</td>
</tr>
<tr>
<td>Egg, 1 large (vitamin D is found in yolk)</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Cheese, Swiss, 1 ounce</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DV = daily value**
These foods are sources of vitamin D₃, cholecalciferol. There are few natural sources of vitamin D₂, ergocalciferol. Wild mushrooms, sun-dried mushrooms, and commercially grown mushrooms that have been treated with ultra-violet light are reasonably good sources of vitamin D₂.³

**Sunlight as a Source of Vitamin D**

Foods can be an important source of vitamin D, but approximately 80-90% of our vitamin D is obtained by exposure to UVB radiation from sunlight.⁴ Age, altitude, cloud cover, latitude, season, skin pigmentation, smog layer, time of day, and the use of sunscreen can all affect the amount of sunlight that is received and the production of vitamin D; additionally, these variables make it difficult to know how much exposure to the sun is needed to produce vitamin D. A striking example is that people living in equatorial areas in which there is a high level of sunshine have been found to be vitamin D deficient. Whereas, elderly adults in a temperate climate (a population less exposed to the sun and with less opportunity to synthesize vitamin D) were able to significantly increase serum levels of vitamin D by regular participation in certain outdoor activities.⁵,⁶

The amount of sunlight that is needed to synthesize an adequate amount of vitamin D has been estimated to be 5-30 minutes, three times week, with the arms, back, face, and legs receiving the most exposure.⁷ Over-exposure to the sun will not produce an excess amount of vitamin D as too much sunlight degrades both vitamin D₃ and pre-vitamin D.⁸

**Daily Vitamin D Requirement and Serum Levels**

The recommended daily dietary intake of vitamin D varies somewhat depending on age and gender. Not all authoritative sources agree on the optimal daily intake of vitamin D, but most sources agree on the following.

- 0-12 months: 10 mcg/400 IU a day
- 1 year-70 years: 15 mcg/600 IU a day
• 71 years and older: 20 mcg/800 IU a day
• Pregnant and lactating females: 15 mcg/600 IU a day

Nutritional supplements of vitamin D usually list the content of D in international units, which is commonly abbreviated as IU. An international unit (IU) is an arbitrary amount that reflects the amount of a nutrient that is needed to produce a biological effect. The microgram amount of an IU varies depending on the substance. For example, an IU of vitamin D is equal to 0.25 mcg of ergocalciferol or cholecalciferol.

Vitamin D serum levels measure the amount of 25-hydroxyvitamin D/calcidiol, the major circulating form of vitamin D. The serum levels of vitamin D that have traditionally been used to identify normal, deficient and toxic states are listed below as:
• 0-25 nmol/L - Deficiency
• >25-50 nmol/L - Insufficiency
• >50-70 nmol/L - Hypovitaminosis
• >70-250 nmol/L - Adequate
• 250nmol/L - Toxic

The serum levels of vitamin D as listed here were derived from population studies; and, they are thought to represent the levels at which calcium absorption declines or parathyroid hormone levels increase. It is generally agreed in the medical/scientific community that very low vitamin D levels of 0-25 represent a significant risk factor for poor bone health. However, the optimal vitamin D level that will promote bone health is not clearly known, and is a matter of some controversy.9

The Institute of Medicine recommends maintaining a serum level >50 nmol/L to have healthy bones. However, the National Osteoporosis Foundation, the American Geriatric Society, and other professional organizations recommend a
level of at least 75 nmol/L,\textsuperscript{10} and some researchers have suggested that the optimum level of vitamin D should be even higher. It is also not clear what the optimal vitamin D level is for maintaining and promoting the health of other organ systems. Most researchers define vitamin D deficiency as a serum level of < 50 nmol/l, but not all do. At this point there are more questions than answers.

**Vitamin D Deficiency**

Vitamin D deficiency is very common in the adult and the pediatric population.\textsuperscript{11} The prevalence of vitamin D deficiency, defined in some population and epidemiological studies as a serum vitamin D level as < 30 nmol/L, has been estimated to be 69.5% in the United States and 86.4% in Europe.\textsuperscript{12} If the serum level defined as representing deficiency is lowered to 20 nmol/L then 41.6% of U.S. adults would be found to be vitamin D deficient;\textsuperscript{13} and, Holick (2007) estimated that approximately 1 billion people worldwide had vitamin D levels less than 50 nmol/L; and, that 40-100% of elderly adults in the U.S. living in the community were vitamin D deficient.\textsuperscript{14}

Regardless of the level that is used to define vitamin D deficiency, it is characterized by hypocalcemia and hypophosphatemia. The basic causes of vitamin D deficiency are listed below as:

1) Decreased intake  
2) Decreased absorption  
3) Decreased synthesis by the kidneys, liver, or skin  
4) Increased breakdown by the liver

There are specific risk factors for vitamin D deficiency,\textsuperscript{1,15,16} which include those outlined below.
1. Decreased intake

2. Inadequate sunlight exposure:
   The elderly and people who are hospitalized or institutionalized are at risk for decreased sunlight exposure.

3. Advanced age:
   The elderly have a decreased ability to synthesize and store vitamin D. The elderly are less likely to be exposed to the sun and for unclear reasons the elderly are less likely to consume foods that have vitamin D.

4. Excessive use of sunscreen and/or covering large areas of the skin with clothing:
   The use of a sunscreen with a sun protection factor of 15 and higher will decrease skin synthesis of vitamin D₃ by 99%.

5. Obesity

6. Dark skin pigmentation

7. Extensive burns:
   People who have had extensive burns are likely to be vitamin D deficient.

8. Chronic kidney or liver disease:
   Significant liver and/or kidney disease can cause decreased production or abnormal excretion of calcidiol and calcitriol.

9. Cystic fibrosis:
   Vitamin D deficiency is almost universal in people who have cystic fibrosis, due to inadequate intake, inadequate sunlight exposure, and decreased absorption through the gut.
10. Fat malabsorption syndromes:
   People who have celiac disease, those who have had gastric bypass surgery or other types of gastric surgery, and people who have diseases of the pancreas or small bowel are likely to have vitamin D deficiency.

11. Sedentary life style

12. Infants who are exclusively breast-fed

13. Low level of high-density cholesterol

14. The use of certain medications such as anti-epileptics and glucocorticoids.
   (Note: The interaction between medications and vitamin D and the effect of medications on vitamin D levels will be discussed later in the learning module).

Many infants are breast-fed, dark skin pigmentation is a risk factor that cannot be altered, and obesity is very common. Therefore, these risk factors of vitamin D deficiency will be discussed in more detail in the next sections.

**Breastfed Infants**

The incidence of vitamin D deficiency in breast-fed infants is quite high and has been estimated to be between 43-70%, depending on the definition of deficiency and the latitude. The American Academy of Pediatrics (APA) recommends that children who are less than six months old should not be directly exposed to the sun, thus removing the most important source of vitamin D. Also, breast milk has between 20-80 IU/L of vitamin D, while fortified infant formula has between 270-677 IU/L of vitamin D.

The lack of infant exposure to sunlight and the low vitamin D content of breast milk can result in vitamin D deficiency. The APA recommends that infants who are
exclusively breast-fed should receive 400 IU of vitamin D daily. This form of supplementation or increasing the mother’s vitamin D intake has been proven to increase serum vitamin D levels in infants.\textsuperscript{17,18}

**Skin Pigmentation**

Low levels of serum 25-hydroxyvitamin D/\textit{calcidiol} and low levels of vitamin D-binding protein are much more common in black Americans than in white Americans.\textsuperscript{19} It has been estimated that less than 10\% of black and Latino Americans are vitamin D sufficient,\textsuperscript{20,21} and, in particular, the number of American black mothers that are vitamin D deficient has been found to be very low. This association with race and vitamin D deficiency is well established and well known, but what is not clear is why it occurs and how it affects the health status of these populations.

The decrease in milk consumption, avoiding exposure to the sun to prevent skin cancer, and the use of sunscreens may explain part of the high incidence of vitamin D deficiency in black and Latino Americans. However, other factors are almost certainly involved, such as, melanin content of the skin, lactose mal-digestion, and obesity.

Vitamin D synthesis in the skin is dependent on skin exposure to UVB radiation, but vitamin D synthesis in the skin is also dependent on the \textit{melanin} content of the skin. Melanin absorbs UVB and people with high melanin content who live in temperate latitudes and that practice sun avoidance may not get sufficient UVB to produce an adequate level of vitamin D.\textsuperscript{22}

There are hereditary and cultural dietary considerations that need to be taken into account when evaluating a patient for vitamin D deficiency. Approximately 80\% of black Americans are lactose mal-digesters and would be likely to avoid vitamin D fortified milk, a major source of vitamin D.\textsuperscript{22} Additionally, obesity is more common in black Americans and obesity is a risk factor for vitamin D
deficiency; there is an inverse relationship between body mass index (BMI) and vitamin D levels.\textsuperscript{23} However, researchers have found that even after controlling for the factor of body fat, black Americans have lower serum levels of vitamin D than do white Americans.\textsuperscript{22}

**Obesity**

Obesity is also associated with vitamin D deficiency.\textsuperscript{23-25} Body mass index, body fat, and waist circumference have been found to be inversely related to serum vitamin D levels less than 50 nmol/L.\textsuperscript{23} The same study reported that 88\% of obese subjects were vitamin D deficient, but only 31\% of the non-obese subjects were vitamin D deficient.

Bellan, \textit{et al.}, (2014) found that 95\% of the severely obese patients studied had serum vitamin D levels that were defined as deficient or insufficient, or less than 20 or 30 nmol/L, respectively.\textsuperscript{26} Although many researchers have found an association between obesity, none as yet have discovered a definitive reason as to why this association occurs.\textsuperscript{11,27,28} It is possible that people who are obese receive less sunlight, do not eat enough vitamin D-fortified foods, and sequester vitamin D in fat.\textsuperscript{28} However, it is not known whether obesity is in part caused by vitamin D deficiency or if vitamin D deficiency is simply an effect of obesity.

**The Health Effects Of Vitamin D Deficiency**

In recent years there has been a considerable amount of research that has investigated the health effects of vitamin D deficiency. As mentioned earlier, vitamin D deficiency has been associated with several disease states, such as auto-immune disorders, cancer, cardiovascular, diabetes, infectious, kidney, neurological, and respiratory diseases, in addition to a corresponding increased risk of death.\textsuperscript{12,29,30} However, at this point, with the exception of the clear and well-established link between vitamin D deficiency and bone integrity, the effects of vitamin D deficiency are unclear.
Certainly, there are epidemiological and observational studies that show a consistent association between low levels of vitamin D and systemic diseases. There are well outlined mechanisms by which vitamin D could influence systemic inflammation, the immune system, cell growth and differentiation and thus affect systemic health. However, definitive cause and effect relationships between vitamin D deficiency and autoimmune diseases, cancer, cardiovascular disease, or any of the other conditions listed above, have not been found. The possibility exists that a low level of vitamin D is an effect, and not a cause.

The list of systemic health effects that have been associated with vitamin D deficiency is exhaustive, and no organ system seems to be exempt. A comprehensive discussion of all of these would not be feasible in this study module, however, some basic information is provided here on a selected number of systemic effects/diseases that may be affected and/or caused by vitamin D deficiency.

**Bone Health: Osteomalacia/Rickets**

Vitamin D deficiency is a cause of *ostemalacia*, a bone disease that is commonly called rickets when it occurs in children. Osteomalacia/rickets is characterized by demineralized bone. Patients with this disease typically have bone pain, muscle weakness, difficulty walking, and several distinctive radiographic findings. In the early stages of the disease the symptoms can be intermittent and non-specific, and the patient may not have any complaints.

Osteomalacia/rickets that is caused by nutritional vitamin D deficiency or by lack of exposure to sunlight is a rare disease, but there is some evidence that the incidence of rickets is increasing. Risk factors for rickets include dark skin pigmentation, inadequate vitamin D supplementation of the child or the mother, the exclusive use of breastfeeding, and inadequate exposure of the child or the nursing mother to sunlight. If the disease is not detected and treatment is delayed, the patient can have fractures and significant skeletal deformities.


Autoimmune Diseases

Low serum levels of vitamin D have consistently been associated with type 2 diabetes, type 1 diabetes in children and adolescents, and multiple sclerosis (MS), all of which are considered to be autoimmune diseases. A low level of vitamin D is a predictor of an increased risk for developing MS, an increased number of relapses, and a more rapid progression of the disease, and low levels of vitamin D are common in patients who have MS. Similar findings have been reported for type 1 and type 2 diabetes. Researchers have found an inverse relationship between vitamin D levels and the risk of developing type 2 diabetes, insulin sensitivity, and glucose tolerance.

In both diseases there are well-outlined mechanisms that could explain the association between vitamin D deficiency and MS and type 1 and type 2 diabetes. There are vitamin D receptors on various cells of the immune system; and, \textit{in vitro} and animal studies have shown that high levels of vitamin D inhibit activity of these cells while low levels heighten their activity.

Multiple sclerosis being a chronic inflammatory disease, an increased inflammatory state induced by low levels of vitamin D could, possibly, increase the intensity of the disease or accelerate its progression. In type 2 diabetes, animal studies have shown that vitamin D deficiency decreases insulin secretion and adversely affects glucose tolerance by binding to the vitamin D receptors on pancreatic beta cells. This effect, plus an initiation of a pro-inflammatory state and/or an affect on calcium homeostasis may explain the association between vitamin D levels and diabetes, but the results of human studies have been equivocal.

Cancer

Calcitrol plays a part in cell proliferation, apoptosis, cell differentiation, angiogenesis, inflammation, and metastasis; and, so it is plausible that low serum
levels of vitamin D could influence the growth and progression of cancers. Vitamin D deficiency has been linked to cancers of the bladder, breast, colon, esophagus, kidney, lung, pancreas, thyroid and many other organs. However, some research shows a link between vitamin D and total cancer death rates while other research does not. Cell cultures and animal studies have provided strong evidence for a link between vitamin D intake, calcitrol levels, and the risk of cancer development and progression. Whereas, human trials have been inconclusive and the data they have provided has been inconsistent.

**Cardiovascular Disease**

Observational research and longitudinal studies have associated Vitamin D deficiency with an increased risk for developing angina, congestive heart failure (CHF), coronary artery disease (CAD), hypertension (HTN), myocardial infarction (MI), stroke, and transient ischemic attack (TIA). Cell studies and some human studies suggest that a low level of vitamin D can adversely influence the cardiovascular system by increasing vascular stiffness and vascular function, affecting platelet function and the renin-angiotensin-aldosterone system, and negatively affecting mortality rate in patients who have CHF or have suffered a MI. However, despite the evidence provided by this and other research, it is still not known whether vitamin D deficiency is a cause of cardiovascular disease or an effect of these pathologies.

Recent evidence suggests that there is an association between blood pressure and vitamin D status. More research is needed to determine more specifically what level of vitamin D and in what sub-populations it has its effect on blood pressure.

Strokes are also related to vitamin D levels. Those with the lowest level of vitamin D are at increased risk for fatal stroke. In addition, vitamin D supplementation may reduce the risk of a future stroke.
Cognitive Impairment, Dementia and Alzheimer’s Disease

Low levels of vitamin D have been associated with an increased risk of developing cognitive impairment, dementia, and Alzheimer’s disease,\(^{58-60}\) perhaps as a result of vitamin D deficiency on the cardiovascular supply to the brain. However, these are associations and many older adults with low levels of vitamin D do not develop Alzheimer’s disease or another neurological impairment.

Drug Interactions With Vitamin D

Drug interactions with vitamin D could occur when:

1) The drug affects the absorption of the vitamin D, either enhancing or inhibiting absorption.
2) The drug interferes with the metabolism by way of the cytochrome P450 enzyme system.
3) When calcium-sparing medications are used along with vitamin D.

A recent (2013) review of the literature examined the evidence for interactions of commonly used medications with vitamin D.\(^ {61}\) Many of these interactions are listed in widely used drug information sources, but it appears that in most cases the connection is tenuous and unproven. However, it is reasonable to be aware of these possible interactions, identify patients at risk and, in selected cases, modify drug therapy and/or monitor patients low of high levels of vitamin D.

Bile Acid Sequestrants

Colestipol and cholestyramine are used to bind to bile acids and lower serum cholesterol. These drugs could bind fat-soluble vitamins, but the majority of the clinical data (albeit a small amount) does not support this.
Lipase Inhibitors

Orlistat is an inhibitor of gastric and pancreatic lipase. Lipase is an enzyme that catalyzes the hydrolysis of fats, a metabolic step that is needed for their absorption; and, because of this mechanism of action it has been suggested this drug could interfere with the absorption of fat-soluble vitamin D. There is evidence that serum 25(OH) D can be reduced by Orlistat therefore monitoring of 25(OH) D levels in patients taking Orlistat would be prudent.

Statin Drugs

The statin drugs reduce cholesterol synthesis and cholesterol is needed for vitamin D synthesis. The statin drugs also may compete for CYP3A4, a cytochrome P450 enzyme that is used by the liver for the conversion of cholecalciferol and ergocalciferol. The data on the effect of the statin drugs on vitamin D level does suggest that atorvastatin can increase 25(OH) D levels, but that pravastatin does not and the authors of this review article found only five studies and their quality was considered to be either neutral or negative).

Anti-tubercular Drugs

Vitamin D deficiency has been associated with and increased susceptibility to tuberculosis and with reactivation of latent infections. However, Lexicomp, a widely used and actively updated source of drug information does not list an interaction between cholecalciferol, ergocalciferol and isoniazid or rifampin. The 2013 review examined six small studies that addressed this issue; all were considered to be of negative quality, most (four) found that vitamin D levels decreased, but there was no control for sun exposure. In addition, the reviewers noted that patients with tuberculosis had low vitamin D levels before being treated with these antituberculars.
**Antiepileptic Drugs**

Osteopenia and osteoporosis have long been associated with the use of anti-epileptic drugs. It is difficult to draw conclusions from the published studies that examined the effect these drugs have on vitamin D levels. Most of the literature - but not all - did show that patients who were taking an anti-epileptic drug or drugs did have lower vitamin D levels than patients who were not. However, the studies that examined the effect of a single antiepileptic did not find lower serum vitamin D levels when compared to control subjects. The reviewers felt that low vitamin D levels that were associated with the use of anti-epileptics were most likely due to lack of sunlight or dietary deficiency.

**Glucocorticoids**

Osteoporosis has long been known as an adverse effect of drugs such as prednisone, hydrocortisone, and dexamethasone. Researchers have not found that the glucocorticoids consistently and significantly affect vitamin D levels.

**Immunosuppressive drugs**

Cyclosporine and tacrolimus are used for patients who have had an organ transplant and for the treatment if immunosuppressive diseases such as rheumatoid arthritis. Osteoporosis is a common long-term side effect of these drugs, but the few studies that examined the effect cyclosporine and tacrolimus have on vitamin D have not shown a strong association between the use of these drugs and low serum vitamin D levels.

**Histamine$_2$ – Receptor Antagonists**

Animal studies have shown that cimetidine is an inhibitor of enzymes that are involved in converting cholecalciferol and ergocalciferol to 25 (OH) D, but one small human study provided only confusing results. Patients taking cimetidine did
not develop a decrease in their serum vitamin D levels from baseline, but when the patients stopped taking cimetidine their serum vitamin D levels increased.

**Thiazide Diuretics**

The thiazide diuretics decrease renal excretion of calcium and it is reasonable to assume that taking one of these drugs and a vitamin D supplement would elevate serum calcium levels. Three cases have been reported that supported this - the patients were taking vitamin D and a thiazide diuretic and developed hypercalcemia - but the other literature reviewed did not find that the thiazide diuretics increased serum vitamin D levels. The reviewers concluded that the concomitant use of a vitamin D supplement and a thiazide diuretic could cause hypercalcemia and that the elderly and/or people with decreased renal function or hyperparathyroidism may be especially vulnerable.

**Highly-Active Anti-Retroviral Therapy (HAART)**

The drugs used for HAART can inhibit or induce CYP3A4. However, at the time of the review there was no conclusive evidence that HAART negatively affects vitamin D levels.

**Vitamin D Toxicity: Acute And Chronic**

Toxicity from vitamin D, either acute toxicity or chronic, is rare. Vitamin D is lipophilic, rapidly removed from circulation and sequestered in fat, and it has a long half-life. Because of these properties, toxicity from vitamin D usually results from chronic over-ingestion of high supplemental doses. Acute toxicity is quite rare, and the case reports of acute toxicity seem to involve at least several days of excessive ingestion.62,63
Chronic vitamin D toxicity, although rare, is well known and well described. The primary effect of vitamin D intoxication is hypercalcemia. If the serum calcium is < 12 mg/dL this is considered mild; if it is between 12-14 mg/dL it is considered moderate; and, if > 14 mg/dL it is considered severe. However, the risk of toxicity and the signs and symptoms associated with each serum calcium level will also be influenced by the patient’s age, and the duration of the hypercalcemia. It is common for patients with vitamin D intoxication to be anorexic, lethargic, fatigued, and dehydrated. Excess calcium acts as a diuretic and also causes nausea and vomiting, and serious symptoms such as obtundation, renal impairment and seizures may be seen.

What is not well known is how much vitamin D is required to produce intoxication. The recommendations for dietary intake of vitamin D and serum vitamin D levels assumed minimal sun exposure. The upper limit for daily intake has been estimated to be 4000 IU. Several sources indicate that doses of 10,000 IU daily may be safely used and it is quite easy to obtain 10,000 IU of vitamin D per day by exposure to sunlight. However, doses that are considered normal and therapeutic have produced toxicity, much higher doses (up to 100,000-200,000 IU a day and higher) have been used without producing vitamin D toxicity and hypercalcemia.

A 2014 review notes that most cases of pediatric intoxication involve doses of 240,000 IU - 4,500,000 IU per day. The serum level that defines vitamin D intoxication has been estimated to be > 375 nmol/L. The treatment for vitamin D intoxication is identified below:

1) Discontinue the vitamin D supplementation.
2) Fluid replacement.
3) Cautious use of loop diuretics to increase calcium excretion.
4) The use of biphosphonates to decrease bone resorption and release of calcium into the serum.
5) The use of calcitonin, which decreases bone resorption of calcium, blocks the release of calcium into the serum, promotes renal excretion of calcium and antagonizes the physiological effects of parathyroid hormone.

6) In severe cases hemodialysis may be needed.

**Prevention And Treatment Of Vitamin D Deficiency:**

**Therapeutic Use Of Vitamin D Supplementation**

In individuals that are not vitamin D deficient the daily requirement for vitamin D can be obtained by exposure to sunlight and by dietary intake. Direct sunlight exposure is an easy way to get vitamin D. Individuals who get 10-30 minutes of sunlight between 10 am and 3 pm, two times a week, will most often have enough vitamin D. It does not require full body sunbathing to get vitamin D. Exposing the arms and face allows the body to acquire adequate vitamin D in most individuals. The recommended dietary intake of vitamin D was discussed earlier in this learning module. Routine screening of the general population for vitamin D deficiency by primary care is not recommended; however, as ongoing research outcomes on the health benefits of vitamin D evolve the general guidelines for screening deficiency may change. For now, only individuals considered at risk, for example, elderly or those with osteoporosis, are recommended for screening of vitamin D deficiency.

The value of supplemental vitamin D for disease prevention and/or modification of disease progress are not clear at this time. Although low serum vitamin D levels may be a risk factor for the development of chronic diseases and influence the course of those diseases, there is no firm evidence at this time that vitamin D supplementation is helpful for people with autoimmune diseases, cardiovascular diseases, cancer, or other pathologies.
Recommending vitamin D supplementation as a standard health prevention strategy is complicated because there is no absolute consensus on the optimal vitamin D level, how to measure it, and what doses are effective and safe. However, there are guidelines for the treatment of vitamin D deficiency. Either cholecalciferol or ergocalciferol can be used, but a meta-analysis of seven randomized trials found that cholecalciferol was more effective at elevating serum vitamin D levels.

**Learning Break:** The vitamin D metabolites calcidiol and calcitrol can be used to treat vitamin D deficiency, as can artificial UVB. However, these drugs are typically second-tier choices and using artificial UVB is difficult because there is no established safe dose. These therapies will not be discussed in detail.

The following dosing regimens are from the Endocrine Society, the National Osteoporosis Foundation, the National Kidney Foundation, and other professional resources.

**Endocrine Society Guidelines**

1. People who are obese, people who have malabsorption syndrome and are vitamin D deficient, or people who are taking medications that may affect vitamin D levels: 6000-10,000 IU a day to attain a serum level of 75 nmol/L, then a maintenance dose of 3000-6000 IU a day.

2. Adults who are vitamin D deficient: 50,000 IU once a week for eight weeks or 6000 IU a day for eight weeks. This should be followed by a maintenance dose of 1500-2000 IU a day. The goal is to reach and maintain a serum level of 75 nmol/L.
3. Children 1-18 years who are vitamin D deficient: 50,000 IU a week for at least six weeks or 2000 IU a day for at least six weeks. This should be followed by a maintenance dose of 600-1000 IU a day. The goal is to reach and maintain a serum vitamin D level of 75 nmol/L.

4. Children 0-1 years: 2000 IU a day for six weeks or 50,000 IU a week for six weeks. This should be followed by a maintenance dose of 400-1000 IU a day. The goal is to reach and maintain a serum level of 75nmol/L.

**National Osteoporosis Foundation Guidelines**

Osteoporosis prevention, adults ≥ 50 years: Cholecalciferol or ergocalciferol, 800-1000 IU a day.

**National Kidney Foundation**

Vitamin D deficiency/insufficiency in patients with chronic kidney disease stages; Oral treatment duration should be a total of 6 months:

1. Serum 25 (OH)D < 12.5 nmol/L: Ergocalciferol, 50,000 units/week for 12 weeks, then 50,000 units/month.
2. Serum 25(OH)D 12.5-37.5 nmol/L: Ergocalciferol, 50,000 units/week for 4 weeks, then 50,000 units/month.
3. Serum 25(OH)D 40-80 nmol/L: Ergocalciferol, 50,000 units/month.

**Osteomalacia, Familial Hypophosphatemia, and Rickets**

1. Hypoparathyroidism: Ergocalciferol, 25,000-200,000 IU a day and calcium supplements.
2. Nutritional rickets and osteomalacia: Adults with normal absorption, ergocalciferol, 1000-5000 IU a day.
3. Adults with malabsorption: Ergocalciferol, 10,000-300,000 IU a day.
4. Vitamin D-dependent rickets: Ergocalciferol, 10,000-60,000 IU a day.
5. Vitamin D-resistant rickets: Ergocalciferol 12,000-500,000 IU a day
6. Familial hypophosphatemia: Ergocalciferol 10,000-60,000 IU a day plus phosphate supplements.

The contraindications for the use of vitamin D are hypercalcemia, malabsorption syndrome, and vitamin D toxicity. Adverse effects are related to elevated vitamin D levels.

Vitamin D does enter breast milk. Caution should be used when prescribing vitamin D supplementation to breastfeeding mothers, and vitamin D is considered to be category D for pregnancy.

**Summary**

Vitamin D is an essential nutrient that is needed for normal calcium and phosphorus metabolism. It is synthesized in the skin by exposure to sunlight and it is ingested in the daily diet. The recommended daily allowance for vitamin D is currently considered to be 600 IU a day, 400 IU a day for children 0-12 months and 800 IU a day for adults ≥ 71 years. In recent years, vitamin D has been the subject of intense scrutiny. Researchers have tried to determine: 1) How much vitamin D is needed for optimal health; 2) How much is needed to treat certain diseases and certain populations; 3) The health effects of vitamin D deficiency, and why vitamin D deficiency is so widespread, and; 4) How much vitamin D is safe and how much is toxic. Despite the attention focused on vitamin D, the knowledge that has been gained is out-shadowed by questions that remain.

Vitamin D deficiency is widespread (that is not disputed), but it is still not known precisely why so many people have low serum levels of vitamin D and how vitamin D deficiency affects health. Epidemiological studies have consistently shown an association between vitamin D deficiency and the development of many
chronic diseases and the progress of chronic diseases. However, definitive proof of a cause and effect relationship has remained elusive. If we accept that vitamin D deficiency can *cause* chronic diseases and it is not an *effect* of chronic diseases than supplementation would be expected to prevent and/or treat illness. However, research that has focused on vitamin D supplementation as a preventative measure or as a treatment has yielded ambiguous results.

Individual risk factors for vitamin D deficiency need to be more clearly defined and understood. The recommended daily allowance for vitamin D has been set, but there is still research that needs to be done to determine exactly how much vitamin D should be used for treating specific diseases and certain patient populations. The amount of vitamin D that is safe is not entirely clear nor is the amount that is toxic. Vitamin D intoxication is well known and well described, but the reported amounts that are safe or toxic vary considerably. There appear to be genetic variations in vitamin D metabolism that affect individual susceptibility to intoxication from vitamin D, but they are not completely understood.

Vitamin D deficiency is common. Nurses need to know that this nutritional deficiency is widespread, understand which patient populations are potentially at risk, and know the chronic diseases that may be caused and/or influenced by vitamin D deficiency. Finally, nurses need to know why vitamin D is needed, how vitamin D is obtained and be able to advise patients about the basics of vitamin D as it relates to their diet and health.

*Please take time to help NurseCe4Less.com course planners evaluate the nursing knowledge needs met by completing the self-assessment of Knowledge Questions after reading the article, and providing feedback in the online course evaluation.*

*Completing the study questions is optional and is NOT a course requirement.*
1. Vitamin D is obtained by:
   a. exposure to sunlight and dietary intake
   b. exposure to sunlight
   c. dietary intake
   d. ingestion of manufactured supplements

2. One of the primary functions of vitamin D is:
   a. control of muscle contraction
   b. control of calcium and phosphorus metabolism
   c. control of potassium and sodium metabolism
   d. control of renal blood flow

3. Good dietary sources of vitamin D are:
   a. whole grains and fruits
   b. leafy green vegetables and red meat
   c. fortified milk and certain fishes
   d. citrus fruits and nuts

4. Vitamin D deficiency is characterized by:
   a. hypokalemia
   b. hyponatremia
   c. hypomagnesemia
   d. hypocalcemia

5. True or false: Vitamin D excess can be caused by over-exposure to sunlight.
   a. True
   b. False
6. Risk factors for vitamin D deficiency include:
   a. excessive exposure to sunlight, malabsorption syndrome, obesity
   b. poor dietary intake, cardiac disease, multiple sclerosis
   c. lack of exposure to sunlight, use of certain medications, obesity
   d. kidney disease, excessive dietary fat, hypertension

7. True or false: Infants who are exclusively breast-fed are at risk for vitamin D deficiency.
   a. True
   b. False

8. Vitamin D deficiency has NOT been linked to which disease?
   a. Osteoporosis
   b. Heart disease
   c. Diabetes
   d. Pneumonia

9. Which of these drugs may influence vitamin D levels?
   a. Statins, anti-epileptic drugs
   b. Beta-blockers, opioid analgesics
   c. ACE inhibitors, glucocorticoids
   d. Calcium channel blockers, non-steroidal anti-inflammatories

10. Vitamin D intoxication is primarily characterized by:
    a. hyperkalemia
    b. hypercalcemia
    c. hypernatremia
    d. hypermagnesemia
Correct Answers:

1. A
2. B
3. C
4. D
5. B
6. C
7. A
8. D
9. A
10. B

References Section

The reference section of in-text citations include published works intended as helpful material for further reading. Unpublished works and personal communications are not included in this section, although may appear within the study text.


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