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AHC Media

Vitamin D: Health and Disease

A few years ago, vitamin E was deemed to be an extremely important nutrient required to maintain health, prevent or delay several disorders, and prolong life. However, many clinical trials involving intervention with supplemental administration of vitamin E failed to establish or confirm these benefits. A similar prominence is being afforded at present to vitamin D because of relationships being documented between vitamin D deficiency and multiple outcomes, including several disorders and mortality. Therefore, supplementation of vitamin D, sometimes even in megadoses, is being implemented presently in clinical practices, although randomized interventional clinical trials of vitamin D supplementation in assessment of various outcomes are yet to be undertaken and completed. It is hoped that vitamin D does not follow the initial enthusiasm and the later failure noted with other nutritional supplements including vitamin E. Therefore, it is an appropriate and opportune time to present a thorough review of vitamin D including its history, its well-established role in maintaining skeletal health, and a recent knowledge about its probable relationship with extraskeletal disorders.

History of Vitamin D

In 1822, Jedrzej Sniadecki noticed that in Poland, farm children did not develop rickets, in contrast to children living in Warsaw, who had high incidence of the disease.[1] The modern history of vitamin D begins in the late 19th century when Theodore Palm, a British medical missionary and epidemiologist, noted through his travels that children living in equatorial countries did not develop rickets.[1] In 1918, Sir Edward Mellanby, searching for a cure for rickets, induced rickets in dogs by keeping them out of sunlight and feeding them exclusively oats.[1] He then fed the rachitic dogs cod liver oil, and cured them of rickets within a few months, thereby confirming that cod liver oil was a source of an essential micronutrient. In the following years, Elmer V. McCollum, a chemist, discovered the compound that is now known as vitamin D by investigating the chemical composition of cod liver oil. The substance originally was classified as a vitamin because of its food source. However, several scientists were able to show that rickets also could be cured by exposure to sunlight or ingestion of ultraviolet (UV)-irradiated cholesterol-containing food. This led to the discovery of 7-dehydrocholesterol (7-DHC), the precursor of vitamin D3, by Windaus and colleagues in 1937. They isolated 7-DHC from animal skin and induced formation of vitamin D3 by irradiating 7-DHC with UV radiation. Windaus received a Nobel Prize for this work, which finally provided a unifying explanation for two competing theories — namely exposure to sunlight and intake of certain foods as the source of vitamin D.[1]

Today, it is well known that the farther away one lives from the equator, the shorter the period of the year during which the intensity of sunlight is sufficient to produce vitamin D3.[2] Therefore, in the United States, most milk products are supplemented with vitamin D. Vitamin D is found naturally in moderate to high concentrations in fish oils and fish liver and in lesser concentrations in eggs.[2]

Executive Summary

Vitamin D has generated considerable controversy over the years. A recent Institute of Medicine report has given guidelines for physicians for management of screening and treatment.

- Vitamin D deficiency typically is defined as a serum 25(OH)D concentration of < 20 ng/mL.
- Meta-analyses of randomized controlled clinical trials provide the strongest evidence for the benefit of vitamin D in prevention of fractures and falls in the elderly.
- Lower all-cause mortality has been observed in individuals with adequate circulating vitamin D levels.
- Screening is recommended in high-risk patients and supplementation schedules to achieve desirable serum concentrations > 30 ng/mL.

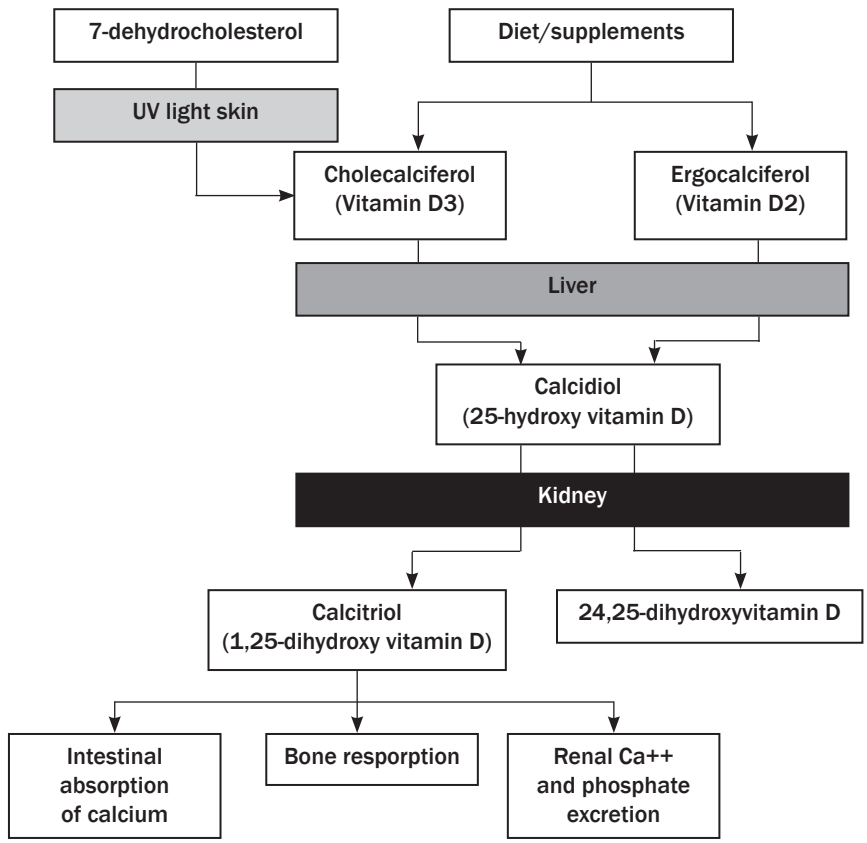
Physiology of Vitamin D

Vitamin D (calciferol) has two forms: vitamin D2, or ergocalciferol, and vitamin D3, or cholecalciferol. Both are produced from sterol precursors.[2] Vitamin D3 is produced in the skin from 7-dehydrocholesterol, a cholesterol precursor present in UV rays (*see Figure 1*). It also is available from certain foods similar to vitamin D2. Both forms are used as dietary supplements as well as for pharmaceutical purposes in disorders of vitamin D deficiency, although vitamin D2 is considered to be less potent than vitamin D3.[2] The two forms differ in their side chains, and both are metabolized similarly (*see Figure 1*). Thus, both are converted to active forms, e.g., 25-hydroxyvitamin D (25(OH)D) in the liver and 1,25-dihydroxyvitamin D (1,25(OH)D) in the kidney, or to inactive forms, e.g., 24,25(OH)D and 1,24,25(OH)D in the same organs, respectively.[2] Their respective serum concentrations are shown in Table 1.

In this article, the term vitamin D will be used to refer to total vitamin D or the sum of vitamins D2 and D3. The total 25(OH)D, which is the sum of 25(OH)D2 and 25(OH)D3, is used to evaluate adequacy of circulating vitamin D derived via sunlight and oral intake, whereas total 1,25(OH)D indicates the most active form circulating in the blood.

The major source of vitamin D is synthesis in the skin.[2] As a result, it is more properly classified as a hormone. Synthesis is stimulated by UVB radiation from sunlight and is reduced by the skin pigment, melanin. 25-hydroxylation of vitamin D occurs in the liver, and is mainly auto regulated by serum concentration of vitamin D; thus, serum 25(OH)D level is a good indicator of total body vitamin D status.[3] In contrast, 1,25-hydroxylation in the kidney is regulated by several factors (*see Figure 1*), including changes in the serum concentrations of parathyroid hormone (PTH), phosphorus, and calcium.[3] A decline in serum calcium

Figure 1: Pathways of Vitamin D Synthesis



Metabolic activation of vitamin D to calcitriol and its effects on calcium and phosphate homeostasis. The result is an increase in the serum calcium and phosphate concentrations.

Table 1: Vitamin D and its Metabolites

Generic Name	Name	Abbreviation	Serum Concentration
Calciferol	Vitamin D	D	1.6 ± 0.4 ng/dL
Ergocalciferol	Vitamin D2	D2	
Cholecalciferol	Vitamin D3	D3	
Calcidiol	25-hydroxyvitamin D	25(OH)D	26.5 ± 5.3 ng/mL (30 – 75)*
Calcitriol	1,25-hydroxyvitamin D	1,25(OH)D	34.1 ± 0.4 pg/mL (18 – 72)*
	24,25-dihydroxyvitamin D	24,25(OH)2D	1.3 ± 0.4 ng/mL
	25,26-dihydroxtvitamin D	25,26(OH)3D	0.5 ± 0.1 ng/mL

*Present normal range in parenthesis

concentration results in an increase in PTH secretion, and each independently stimulates 1,25-hydroxylation of vitamin D in the kidney, as does a decrease in serum phosphorus level. The production is also enhanced, albeit to a modest degree, by insulin-like growth factor-1 (IGF-1). Finally, renal generation of 1,25(OH)D is inhibited primarily by high levels of serum calcium and phosphate, and modestly by fibroblast-derived growth factor 23 (FGF23), a cytokine produced in bone and other tissues.[3] Most of circulating 1,25(OH)D is bound to the protein transcalciferin synthesized in the liver, while a small portion circulates in the free form. Non-hydroxylated vitamin D is stored in adipose tissue.[3]

Perhaps the most well-established action of 1,25(OH)D is to facilitate intestinal absorption of calcium, involving several mechanisms. However, to understand these mechanisms, it is helpful to review the entire process of GI calcium absorption beginning with oral intake. Dietary calcium is actively taken up from the luminal brush border of enterocytes.[3] Subsequently, it binds to a calcium-binding protein (CaBP), and this complex is translocated to the basolateral surface of the cells. Finally, calcium is actively extruded out of the cell by an ATP-dependent calcium pump in exchange for sodium. The calcium pump is maintained by a sodium-potassium exchanger that forces sodium back out of the cell to maintain a sodium gradient.[3] 1,25(OH)D enhances intestinal absorption of calcium by 1) inducing the expression of CaBP on the surface of enterocytes; 2) increasing the permeability of the brush border of the duodenum to enteral calcium; 3) multiplying the number of calcium-sodium exchange pumps in the basolateral enteral membrane; and 4) opening calcium channels via activation of a membrane-bound receptor.[2] Moreover, 1,25(OH)D facilitates phosphorus and magnesium uptake from the gut.[2] Alternatively, in bone, 1,25(OH)D plays a crucial role in calcium and phosphorus mineralization of the osteoid material secreted by osteoblasts. This occurs mostly through its indirect effects of increasing calcium and phosphorus uptake. It also exerts a synergistic effect with PTH in stimulating bone resorption in order to raise serum calcium concentration, although the exact mechanism of this phenomenon has not been defined clearly.[2]

Normal Vitamin D Levels and Diagnosis of Vitamin D Deficiency

Establishing a normal range of serum 25(OH)D levels has been problematic for several reasons:

1. There are differences between methodologies for vitamin D measurement. For example, 25(OH)D may be measured by a radioimmunoassay, enzyme-linked assays, and liquid chromatography with mass spectrometry.[4]
2. The absence of standard calibrators contributes to between-laboratory differences in 25(OH)D measurement.[4] A single serum sample that is analyzed for 25(OH)D concentration by several laboratories has produced differences of up to 17 ng/mL.[5]
3. 25(OH)D levels fluctuate among individuals with different seasons of the year, exposure to sunlight as well as a dietary intake, and these factors are not taken into consideration in most studies.
4. Vitamin D levels vary with amount of adiposity as well as skin pigmentation, with lower levels among the obese and darker pigmented individuals.[6]
5. All available methods to measure 25(OH)D concentrations do not detect both 25(OH)D2 and 25(OH)D3.[5]
6. It is difficult to distinguish between individual effects of vitamin D and calcium, since the two are frequently supplemented together.

Despite these challenges, most reference laboratories define a normal serum concentration of vitamin D as > 30 ng/mL (> 75 nmol/L). This cutoff level is based on cross-sectional studies demonstrating that a minimal circulating serum concentration of 25(OH)D required to suppress PTH is 30 ng/mL.[6] However, a wide variability has been evident with respect to the relationship between PTH and vitamin D

in these studies. In fact, many individuals maximally suppressed PTH with much lower vitamin D levels, whereas some others required more than 30 ng/mL of serum 25(OH)D to maximally suppress PTH. Further studies have been conducted in attempts to define optimal 25(OH)D as the level beyond which there is no further incremental increase in 1,25(OH)D generation, or to define it as the level at which maximal GI calcium absorption occurs.[6] However, similar to the relationship noted between 25(OH)D and PTH, these parameters also failed to conclusively demonstrate a consistent lowest normal serum concentration of 25(OH)D.[6] Nevertheless, most authorities utilize > 30 ng/mL as a normal serum 25(OH)D concentration with a documentation of the estimated prevalence of vitamin D insufficiency and deficiency to the extent of 50% to 80% in the general population, 75% in Caucasians, and almost 90% in people of color.[6] It also is important from the clinical perspective to recognize the established normal serum concentrations in both all circulating vitamin D metabolites, especially the active forms (*see Table 1*).

Vitamin D deficiency typically is defined as serum 25(OH)D concentration of < 20 ng/mL based on observations that individuals with these levels manifest inadequate bone mineralization and therefore are at risk for the development of rickets or osteomalacia.[5] Vitamin D insufficiency, then, is characteristically diagnosed as a serum concentration of between 20-30 ng/mL.[5] However, there is no general universal agreement in terms of these values since a wide variability in 25(OH)D concentrations exists among apparently healthy individuals. For example, in a study of Hawaiian surfers with sun exposure of at least 15 hours a week for the preceding 3 months, 25(OH)D levels ranged from 11-71 ng/mL.[5] Moreover, the validity of this subnormal concentration was questioned in a recent study in which annual administration of 500,000 IU of vitamin D in women of advanced age resulted in an increased risk of falls and fractures despite inducing a rise in 25(OH)D from 20 ng/mL to 48 ng/mL within a month.[5]

Extraskeletal Effects of Vitamin D

The role of vitamin D in maintaining normal serum calcium concentration via its effect on gastrointestinal calcium absorption, renal calcium reabsorption, and bone mineralization is well established. Moreover, its important contribution in preserving bone mineralization and preventing rickets in children and osteomalacia in adults has been well documented for more than a century. Finally, the strongest evidence for the benefit of vitamin D (cholecalciferol) in a daily dose of 800 units in prevention of fractures and falls in elderly once again is well documented in a recent meta-analysis of randomized controlled clinical trials.[7,8] However, the importance of vitamin D in influencing function of several other organs and tissues recently has been investigated since vitamin D receptors have been discovered to be present in many tissues besides bone, kidney, and gut. These tissues include elements of the hematopoietic and immune systems; cardiac, skeletal, and smooth muscle; and brain, liver, breast, endothelium, and skin; as well as several endocrine glands, e.g., pituitary, PTH, pancreatic islets (B cells), adrenal cortex and medulla, thyroid, ovary, and testis.[2] In these tissues, 25(OH)D can be converted to 1,25(OH)D locally, without altering serum 1,25(OH)D concentrations.[5] As a result, 1,25(OH)D may regulate synthesis and secretion of insulin, prolactin, and PTH. In addition, it may promote cytokine synthesis and release, e.g. interleukin-2 (IL-2) from lymphocytes and tumor necrosis factor (TNF) from monocytes.[2] 1,25(OH)D also apparently modulates myocardial contractility and vascular tone as well as hepatic regeneration. Furthermore, it reduces the rate of proliferation of many cell lines, including normal keratinocytes, fibroblasts, lymphocytes, and thymocytes as well as abnormal cells of mammary, skeletal, intestinal, lymphatic, and myeloid origin, suggesting an antineoplastic effect.[2] Differentiation of numerous normal cell types, including keratinocytes, lymphocytes, hematopoietic cells, intestinal epithelial cells, osteoblasts, and osteoclasts as well as abnormal cells of the same lineage is enhanced by 1,25(OH)D.[2] These findings have sparked a considerable interest in the nonskeletal benefits of vitamin D in recent years. The curiosity has resulted in many epidemiological studies demonstrating associations between subnormal serum vitamin D concentrations on one hand and increased mortality as well as prevalence of several disorders on the other. However, the evidence for supplementation with vitamin D in improving outcomes is sparse and far from being noteworthy when compared to the compelling data in terms of the skeletal effects.[5] The discussion of presently available data examining the relationship between serum 25(OH)D concentrations and the aforementioned outcomes is summarized below. However, it is likely to be far from complete because of almost daily publication of new reports in the literature or their presentation at meetings of several medical organizations or symposia worldwide.

Mortality. In a study of elderly adults participating in the National Health and Nutrition Examination Survey (NHANES) III, a lower all-cause mortality rate has been observed in individuals with adequate circulating vitamin D levels in comparison to subjects with vitamin D deficiency.[9] However, this finding was simply an association, and the difference in mortality could be reflective of differences in health and nutrition between the two groups. In a meta-analysis of 18 randomized controlled trials, vitamin D supplementation in postmenopausal women lowered risk of mortality by 7% in the vitamin D deficient group.[10] However, every study did not report mortality rates, and assessment of mortality was not the primary endpoint of all the

studies included in the meta-analysis. Therefore, the mortality reduction in the vitamin D sufficient group may be due to a reporting bias, rendering it insignificant especially in light of a recent finding of a lack of a significant improvement in cardiovascular mortality following vitamin D and/or calcium supplementation.[11]

Diabetes and Hypertension. In a cross-sectional study examining the relationship between low 25(OH)D and prediabetes and prehypertension, 1711 subjects (898 men and 813 women) were selected from the NHANES, 2001-2006.[12] The subjects were healthy, non-Hispanic Caucasians. Prediabetes was determined using the ADA criterion of fasting serum glucose (FSG) of 100-125 mg/dL. Prehypertension was diagnosed as a systolic BP 120-139 mmHg and/or diastolic BP 80-89 mmHg as recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC-7) criteria. Serum 25(OH)D concentration in the 75th percentile (76.3 nmol/L or 30.5 ng/mL) was used as the cutoff between high and low concentrations. Logistic regression was used to assess the effects of low vitamin D levels on the odds for prediabetes and prehypertension. Mean 25(OH)D concentration in the subjects was 65 nmol/L, and was incrementally lower with each decade of life and with increasing body mass index (BMI). Mean 25(OH)D concentration decreased progressively with levels of 66.2, 62.3, and 54.2 nmol/L in subjects with normoglycemia (FSG < 100 mg/dL), prediabetes (FSG 100-125 mg/dL), and diabetes (FSG ≥ 126 mg/dL), respectively. A similar decline in serum 25(OH)D concentration was noted with levels of 67.9, 61.5, and 62.4 nmol/L in subjects with desirable BP (< 120/80 mmHg), prehypertension (systolic BP 120-139 mmHg and/or diastolic BP 80-89 mmHg), and untreated hypertension (BP ≥ 140/90 mmHg), respectively. In subjects with both prediabetes and prehypertension, average serum 25(OH)D concentration was 61 nmol/L, compared with 68.8 nmol/L in subjects with desirable BP and normoglycemia. Mean serum 25(OH)D concentration was even lower at 49.3 nmol/L in subjects with undiagnosed diabetes and untreated hypertension. Thus, this study demonstrated that in healthy, asymptomatic Caucasian adults with mean serum 25(OH)D concentration < 76.3 nmol/L, the odds ratios for prediabetes, prehypertension, or both were significantly greater than 1. Again, it should be noted that the study documents associations only between low vitamin D level and prediabetes and prehypertension; it does not demonstrate that normalizing vitamin D levels with supplementation improves hypertension or hyperglycemia or decreases the risk of developing prediabetes or prehypertension.

In another recent cross-sectional study, investigators examined associations between concentrations of 25(OH)D and concentrations of insulin, glucose, and HbA1c in an adolescent sample population of 1941 subjects aged 12-17 years from the NHANES survey between 2001-2006.[13] This study included diverse population, e.g., 531 Caucasians, 620 African Americans, 632 Mexican Americans, and 158 subjects of another race or ethnicity. Three groups were established according to 25(OH)D levels: deficiency (< 50 nmol/L), insufficiency (50 to < 75 nmol/L), and sufficiency (≥ 75 nmol/L). According to these diagnostic serum concentrations, 31.5 ± 2.1% of the subjects were vitamin D deficient, 48.3 ± 2.0% were vitamin D insufficient, and 20.3 ± 1.6% were vitamin D sufficient. Adjusted concentrations of insulin were approximately 24% lower among male subjects deemed vitamin D sufficient than men diagnosed to manifest vitamin D deficiency. A significant difference was not seen in female subjects. Furthermore, concentrations of vitamin D were inversely correlated with concentrations of glucose only in Mexican American male subjects. Finally, no significant relationship was detected between vitamin D and HbA1c.[13]

In a post-hoc analysis of older women who participated in any of three of the case-control studies of the Women's Health Initiative (WHI) Clinical Trials and Observational Study, 317 (6.2%) of 5140 women with a mean age of 66 developed diabetes over a mean follow-up period of 7.3 years.[14] However, after adjustment for BMI and other risk factors, the relationship between serum concentrations of 25(OH)D and incident diabetes was not significant.[11] Finally, a recent meta-analysis failed to demonstrate a clinically significant impact of vitamin D supplementation on incidence of hypertension or diabetes.[15]

The Metabolic Syndrome. A Canadian study published earlier this year assessed the association of 25(OH)D and PTH with the metabolic syndrome (MetS) and its traditional and nontraditional components.[16] MetS was diagnosed to be present if a subject had three or more of the following criteria: waist circumference ≥ 102 cm for men and ≥ 88 cm for women if of European origin and ≥ 90 cm for men and ≥ 80 cm for women if of non-European origin; serum triglyceride concentration ≥ 1.7 mmol/L or drug treatment for hypertriglyceridemia; serum HDL cholesterol level < 1.0 mmol/L for men and < 1.3 mmol/L in women or drug treatment; systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg or drug treatment for hypertension; and fasting glucose ≥ 5.6 mmol/L or drug treatment for diabetes mellitus.[16] Nontraditional components of MetS included: elevated serum alanine aminotransferase (ALT), used as a surrogate marker for non-alcoholic fatty liver disease (NAFLD); estimated glomerular filtration rate (eGFR), calculated using the Modified Diet and Renal Disease (MDRD) formula, used as a measure of renal function; urinary albumin to creatinine ratio as a determinant of microalbuminuria; and elevations in white blood cell (WBC) or C-reactive protein (CRP) used to assess for the presence of

Figure 2: Wide and Irregular Epiphysial lines and Cupping of the Metaphyses (Arrow), Characteristic Findings of Rickets or Osteomalacia

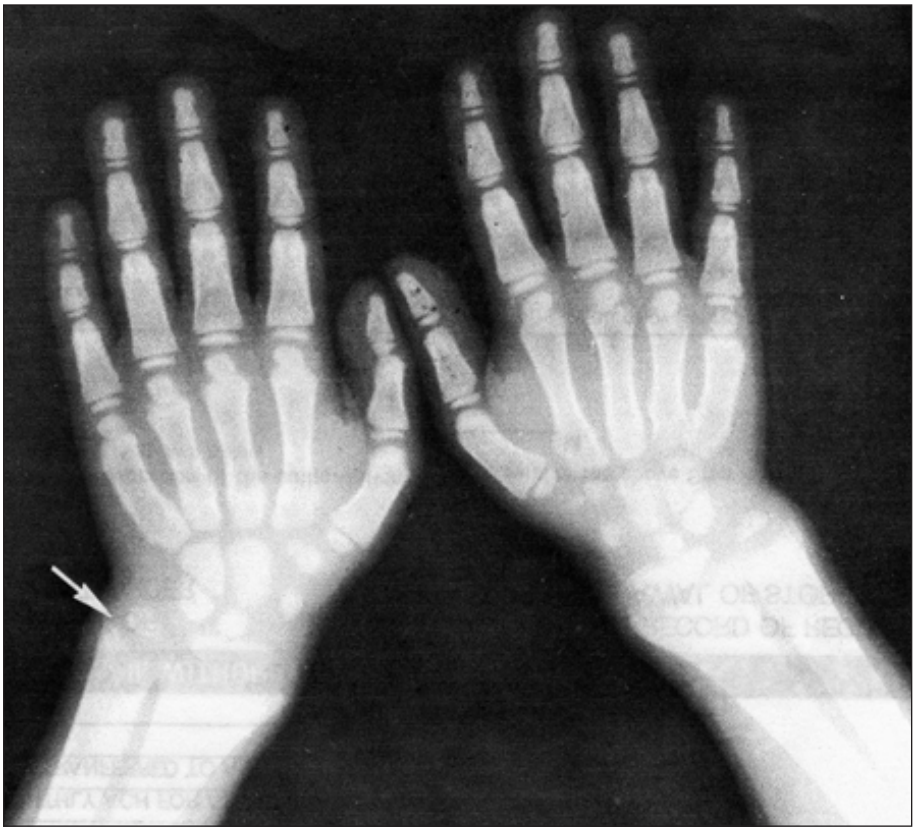
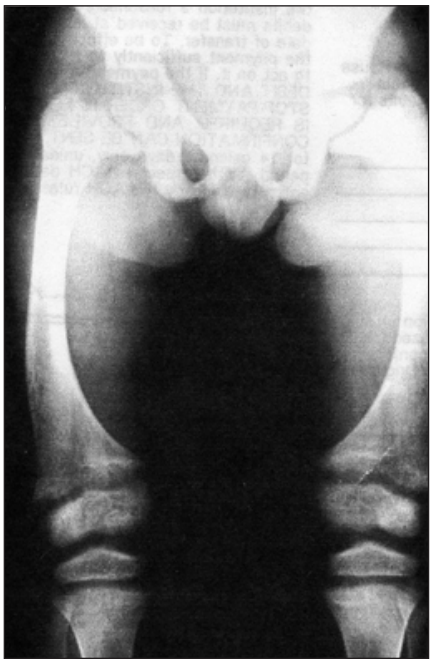


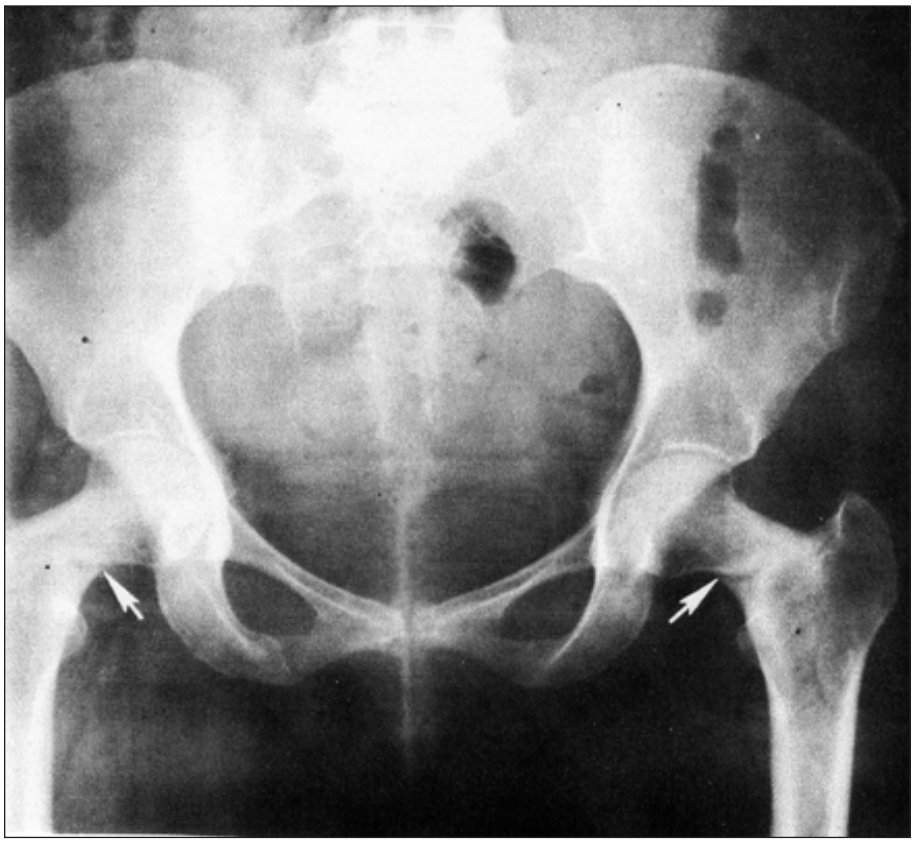
Figure 3: Bowing of Femurs in a Subject with Rickets



inflammation.[16] Normal values for these nontraditional components were based on established clinical guidelines. In this study, 654 subjects, aged ≥ 30 years and who previously had participated in the Prospective Metabolism and Islet Cell Evaluation (PROMISE) cohort, were recruited. All were at high risk for development of type 2 diabetes, but none of them had diabetes at the time of enrollment. Forty-three percent of the participants were classified as having MetS. Serum 25(OH)D decreased progressively with a corresponding rise in serum PTH as the number of MetS components increased. However, PTH was not associated with the presence of MetS after multivariate adjustment.[16] These findings suggest a possible role of 25(OH)D in the pathogenesis of the MetS, but the study does not address the important question whether supplementing with vitamin D decreases the risk of occurrence of MetS, and another recent study showed no significant effect in lowering incidence of MetS.[15]

Coronary Heart Disease Risk. Vitamin D deficiency also has been shown to be associated with coronary artery calcification (CAC), a marker of coronary artery plaque burden and a predictor of coronary events.[17] In a study conducted at the University of Colorado School of Public Health, investigators examined the relationship among serum 25(OH)D concentrations, polymorphisms in vitamin D-associated genes, and the presence and progression of CAC in adults with type 1 diabetes.[17] Three hundred seventy-four non-Hispanic white subjects with type 1 diabetes were examined at baseline, at 3-year, and 6-year follow-up visits. Height, weight, BMI, waist and hip circumferences, BP, smoking history, and dietary intake of vitamin D and calcium were documented at initial visit. Vitamin D levels were classified as sufficient (25(OH)D > 30 ng/mL), insufficient (25(OH)D 20-30 ng/mL), or deficient (25(OH)D < 20 ng/mL). Total cholesterol, HDL cholesterol, triglycerides, and calculated LDL-cholesterol were determined. Genomic DNA was extracted from leukocytes and various vitamin D binding protein polymorphisms and vitamin D receptor gene polymorphisms were genotyped. CAC was measured using electron beam computed tomography at the 3- and 6-year follow-up visits. 25(OH)D concentrations also were determined at 3 years. Vitamin D deficiency and insufficiency were associated with the presence of CAC at the 3-year visit after adjusting for age, gender, and hours of daylight exposure.[17] Adjustment for BMI, HDL-cholesterol, LDL-cholesterol, triglycerides, calcium or vitamin D intake, or various vitamin D binding protein and vitamin D receptor gene at the 3-year visit polymorphisms did not significantly alter these conclusions.[15] In the longitudinal analyses, vitamin D-deficient subjects without preexisting CAC at enrollment were more likely to develop CAC at 3 years than those with vitamin D sufficiency, whereas vitamin D-deficient

Figure 4: Bilateral Pseudo fractures of the Femoral Neck (Arrows), a Pathognomic Finding of Osteomalacia



subjects with CAC already present at initial visit did not experience further CAC progression in comparison to those with vitamin D sufficiency.[17] Among gene polymorphisms, the vitamin D receptor M1T CC genotype appeared to play a role in the effect of vitamin D deficiency and presence of CAC.[17]

Cancer. As mentioned earlier, vitamin D is documented to promote cellular differentiation, inhibit cellular proliferation, and reduce the growth of certain tumors in laboratory animals. In a meta-analysis of case-control studies, with every 20 ng/mL raise in serum 25(OH)D levels, the odds of occurrence of colon cancer were reduced by more than 40%.[18] In other studies, adequate dietary calcium intake is shown to be associated with reduced colon cancer risk and adenoma formation.[19] However, because milk intake is a major determinant of serum 25(OH)D levels, it is difficult to separate the effect of vitamin D from that of calcium intake. In the WHI trial, supplementation with calcium and vitamin D had no significant effect on the risk of colorectal cancer during 8 years of follow-up.[20] However, 8 years may not have been sufficient period of time of observation because colorectal cancer may take many years to develop. With respect to breast cancer, a meta-analysis of several observational studies showed a decreased risk of breast cancer with higher levels of 25(OH)D.[21] However, the WHI randomized clinical trial of calcium and vitamin D supplementation showed no reduction of risk of breast cancer with supplementation.[22] In a meta-analysis of 11 observational studies, prostate cancer was not associated with serum 25(OH)D levels.[5] Similar findings have been reported with respect to the relationship between vitamin D and various other cancers. Thus, no significant benefits of vitamin D supplementation on incidence of various malignancies has been well documented although associations between vitamin D deficiency and prevalence have been evident in some studies.

Similar associations between vitamin D and several other disorders have been reported. One study showed that 28% of women with serum 25(OH)D < 37.5 nmol/L had a primary cesarean section, while only 14% of women with 25(OH)D ≥ 37.5 nmol/L had a primary cesarean section.[23] A cross-sectional study of vitamin D status and muscle function in post-menarchal adolescent girls demonstrated that after correction for weight, positive correlations were noted between 25(OH)D and jump velocity and height, as well as power and force.[24] In another study of young women, negative correlations between 25(OH)D concentration on one hand and visceral and subcutaneous fat, as measured by CT and DEXA, on the other were documented; in women with 25(OH)D ≥ 30 ng/mL, body weight, BMI, and measures of body fat were significantly lower in comparison to those with OH D levels 30 ng/mL.[25] Again, all these studies have merely shown associations between low vitamin D and outcomes and were not designed to demonstrate causality. A recent report has demonstrated a relationship between 25(OH)D levels and neuromuscular and neuropsychological function as well as falls in the elderly men.[26] Reports also have been published regarding associations between 25(OH)D concentrations on one hand and quality of life in patients with inflammatory bowel disease, biomarkers of systemic inflammation, as well as immunological function and disorders on the other.[27-29] Therefore, in the final analysis, the data demonstrating relationships between low 25(OH) D levels and several disorders are rampant, but the evidence regarding improvement in the various outcomes following attaining and maintaining 25(OH)D levels in desirable range with supplementation is scanty.

Disorders of Vitamin D

The disorders of vitamin D include frequently noted deficiency especially

in recent times and the rare syndrome of toxicity (hypervitaminosis D). Historically, vitamin D deficiency was suspected in an individual on presentation of physical signs, e.g., bowing of long bones, costochondral junction thickening, fractures, and/or documentation of radiological changes of rickets or osteomalacia (*see Figures 2-4*). Therefore, vitamin D assessment currently is distinctly indicated as a requirement of testing for subjects manifesting osteoporosis and also probably osteopenia to prevent the consequences seen in the past. Alternatively, since the advent of methodology in determination of serum chemistry panels, low serum calcium and/or low serum phosphorus and/or elevated serum alkaline phosphatase indicated the presence of vitamin D deficiency. Furthermore, vitamin D deficiency is being diagnosed frequently even in asymptomatic, healthy appearing subjects during periodic routine physical evaluations. Finally, the etiology of vitamin deficiency must be determined prior to initiation of its supplementation in an appropriate form (*see Tables 2 and 3*). However, vitamin D supplementation — frequently prior to identifying the cause and that too, even in a high pharmacologic daily dose, ≥ 2000 units of cholecalciferol — has become accepted in some clinical practices, although the evidence for benefits for supplementation with such mega doses is lacking. Commonly recommended initial daily dose of cholecalciferol (D3) is 1000-1200 units with reduction to 600-800 units on attaining the desirable 25(OH) D level. Alternatively, ergocalciferol (D2) may be used with the initial weekly or biweekly dose of 50,000 units with increase in interval of administration to 2-4 weeks on achieving desirable serum 25(OH) D concentration. Calcitriol administration may be required in special situations with lack of conversion of 25(OH)D to 1,25(OH)D (*see Table 4*). In comparison to occurrence of vitamin D deficiency, vitamin D toxicosis is rare especially since milk alkali treatment of acid peptic disease is no longer a practice. However, the occurrence may rise if the practice of administration of megadoses of vitamin D in subjects with deficiency continues over a long term. The other form of vitamin D excess is a rise in level of 1,25(OH)D in some patients with granulomatous disorders, i.e., sarcoidosis, tuberculosis, or histoplasmosis, and infrequently

Table 2: Causes of Rickets or Osteomalacia

Vitamin Deficiency
Low 25(OH)D
Lack of exposure to sunlight
Lack of oral intake
Lack of gastrointestinal absorption
• Fat maldigestion and malabsorption
- Pancreatic disease
- Biliary disease
- Intestinal disorders
Low hepatic 25 Hydroxylase
• Hepatic disorders
Decreased activation of hepatic 25 hydroxylase by drugs, e.g., anticonvulsants, steroids
Low 1,25(OH)D
Renal dysfunction
Hypophosphatemia
• Decreased phosphate intake
• Decreased gastrointestinal absorption
- Vitamin D deficiency
- Therapy with aluminum hydroxide
• Increased urinary excretion
- Primary hyperparathyroidism
- Secondary hyperparathyroidism
- Renal tubular acidosis
Hypoparathyroidism
Congenital lack of 1,25 hydroxylase (Type 1 vitamin resistance or dependence)
Vitamin D resistance
Type 1 with lack of 1,25 hydroxylase
Type 2 with "true" resistance to 1,25(OH)D

Table 3: Vitamin D Resistant or Dependent Rickets

Type	Genetic Transmission	Pathogenesis	Response to 1,25(OH)2D
I	X-linked dominant	Defective gastrointestinal and renal phosphate transport	No
II	Autosomal recessive	Defective renal synthesis if 1,25(OH)2D	Yes

Table 4: Commonly Used Vitamin D Metabolites and Analogs

	Ergocalciferol	Cholecalciferol	Dihydrotachysterol	Calcidiol	Calcitriol
Abbreviation	D2	D3	DHT	25(OH)D3	1,25(OH)2D
Dose	50,000 units Q 1-4 weeks	600-1200 units/ day	25 ug-1 mg/day	1-200 mcg/	0.25 mcg/day day
Duration of Action	1-3 months	1-3 months	1-4 weeks	2-6 weeks	2-5 days
Clinical Indications	Vitamin D Deficiency Vitamin D Malabsorption Hypopara-thyroidism Anticonvulsant Therapy	Vitamin D Deficiency Vitamin D Malabsorption Hypopara-thyroidism Anticonvulsant Therapy	Chronic Renal Failure Hypopara-thyroidism	Vitamin D Malbsorption Chronic Renal Failure	Chronic Renal Failure Hypopara-thyroidism Hypophos-phatemic Rickets Acute Hypocalcemia Vitamin D-Dependant (Resistant) Rickets Type I and II

with malignancy, i.e., leukemia or lymphoma. In most of these patients, increased levels of 1,25(OH)D are accompanied by rise in serum creatinine and urea nitrogen. The treatment involves administration of prednisone and management of the offending disorder.

Finally, because the ongoing practice of administration of megadoses of vitamin D, as well as the peer pressure, the Institute of Medicine (IOM) recently formed a panel of experts to present a report with formulation of new guidelines regarding determination of daily vitamin D requirement to maintain health and the supplementation dose in subjects with low 25(OH)D levels.

In November 2010, the IOM committee released a report on dietary reference intakes (DRIs) of calcium and vitamin D for the population at large.[30] The committee took a comprehensive look at both skeletal and extraskeletal outcomes of supplementation to: 1) determine outcomes that are affected by supplementation with calcium and vitamin D, 2) determine the appropriate dose of supplementation needed to achieve favorable outcomes, and 3) determine the dose of supplementation to be excessive. After a comprehensive review of the literature, the committee determined that skeletal health was the only outcome for which there is proven evidence of a dose-response relationship with calcium and vitamin D sufficient to warrant DRIs. On the other hand, for extraskeletal outcomes, such as cancer, cardiovascular disease, and diabetes, there was inconsistent evidence of any cause-and-effect relationship. Therefore, the committee deemed the evidence for improving extraskeletal outcomes as insufficient to serve as a basis for DRI recommendations.[30] Based on the estimated average requirements (EAR) corresponding to the median intake needs of the population, the committee concluded that serum 25(OH) D level of 16 ng/mL (40 nmol/L) fulfills the requirements of approximately half the population, and levels of 20 ng/mL (50 nmol/L), which is two standard deviations above the median and would fulfill the requirements of at least 97.5% of the population. The committee observed that although average intake of vitamin D from foods tends to be less than 400 IU/d in the population, mean 25(OH)D levels have been > 20 ng/mL in representative samples. Thus, based on these data and a level of 20 ng/mL identified as a normal level in at least 97.5% of the general population, the committee reached the surprising conclusion that the majority of the North American population currently is meeting its needs for vitamin D. This conclusion may be in contrast to the popular notion that in North America most people are vitamin D insufficient because of a relatively short duration of adequate sun exposure to produce vitamin D, and where the majority of the population avoids sun exposure or wears sunscreen and has a lack of adequate consumption of milk and milk products. The IOM committee also specified tolerable upper intake levels for vitamin D of 4000 IU/d for ages 9 and older without inducing toxicity. This amount of intake corresponds with a 25(OH) D level of approximately 50 ng/mL. However, the committee also warned that this amount is not meant to be a target intake, since it is the level beyond which risk for harm rises. In concurrence with the IOM, the Endocrine Society also issued guidelines of screening for assessment of serum vitamin D concentrations.[31] These guidelines do not recommend screening for healthy individuals or population at large. The

recommendations include DRI as follows: infants, 400 units; ages 1-70 years including pregnant women, 600 units; and ages ≥ 70 years, 800 units. Screening is recommended to detect vitamin D deficiency or insufficiency in individuals at high risk, e.g., pregnant and lactating women; those with osteopenia or osteoporosis, hepatic disease, renal disease, and diabetes; subjects with obesity including those undergoing bariatric surgery; syndromes of fat maldigestion and malabsorption; or prolonged use of high-risk medications, such as anticonvulsants, antifungal agents, glucocorticoids, and antiretroviral agents. The group recommends vitamin D supplementation for management of subjects with deficiency or insufficiency as described in the section of disorders of vitamin D.

Conclusion

It is well established that vitamin D is an essential for the normal growth, development, and maintenance of bone health. A severe deficiency in vitamin D has been demonstrated to cause rickets in children and osteomalacia in adults. The presence of vitamin D receptors has been demonstrated in several organs in addition to bone, gut, and kidneys, which has led to numerous studies investigating the role of vitamin D in various extraskeletal disorders. However, to date, there are hardly any data demonstrating benefits for extraskeletal disorders following supplementation with vitamin D. An IOM committee and the Endocrine Society conducted a systematic review of the available literature on vitamin D and issued recently almost identical guidelines regarding DRIs, specific criteria for screening individuals to detect deficiency (≤ 20 ng/mL) or insufficiency (20-29 ng/mL), and supplementation schedules to achieve desirable serum concentration (> 30 ng/mL) documented as essential to maximize its effect on calcium, bone, and muscle metabolism.

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2. Evaluate the credibility of published data and recommendations related to primary care medicine;
3. Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

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CME Questions

7. The most active form of Vitamin D is:
   a. dihydrotachysterol.
   b. 25(OH)D.
   c. 24-25(OH)D.
   d. 1,25(OH)D.

8. 1,25(OH)D is generated in:
   a. muscle.
   b. kidney.
   c. brain.
   d. liver.

9. Conversion of 25(OH)D into 1,25(OH) D is enhanced by:
   a. parathyroid hormone.
   b. calcitonin.
   c. growth hormone.
   d. glucagon.

10. Vitamin D deficiency is defined as serum level of 25(OH)D:
    a. < 50 ng/mL.
    b. < 40 ng/mL.
    c. < 20 ng/mL.
    d. < 10 ng/mL.

11. Drugs inducing vitamin D deficiency include:
    a. phenytoin.
    b. acetomenophen.
    c. penicillin.
    d. digoxin.

12. Available oral forms of vitamin D for supplementation in vitamin D deficiency include:
    a. ergocalciferol, vitamin D2.
    b. cholecalciferol, vitamin D3.
    c. calcitrol.
    d. All of the above
    e. None of the above

13. Vitamin D deficiency is an established pathophysiologic factor associated with increased incidence of:
    a. metabolic syndrome.
    b. cancer.
    c. bone deformities.
    d. inflammatory bowel disease.

14. Vitamin D supplementation improves:
    a. glycemic control in diabetes.
    b. hypertension.
    c. lipid profiles.
    d. cardiovascular mortality.
    e. None of the above

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