A MINI-OVERVIEW OF VITAMIN D

By

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Abstract

Generally speaking, vitamins are essential for man and animal. Vitamin D is essential for good overall health and strong and healthy bones. It's an important factor in making one sure of his muscles, heart, lungs and brain…etc. Vitamin D and calcium deficiencies are common world-wide, causing nutritional rickets and osteomalacia, which have a major impact on health, growth, and development of infants, children, and adolescents; consequences can be lethal or can last in-to adulthood. This mini-review gives an overview of vitamin D.

Keywords: Vitamin D, Sources, Deficiency, Repletion, Calcium, Insect allergy, Type 2 diabetes mellitus.

Introduction

Generally, the vitamins are chemically un-related families of organic compounds; essential in small amounts for normal metabo-lism. Because vitamins (with exception of vitamin D) cannot be synthesized by hu-mans, they need to be ingested in the diet to prevent disorders of metabolism. Vitamins are divided into water-soluble and fat-solu-ble (Tab. 1). Vitamin D is a fat-soluble one.

Review and Discussion

Deficiency of vitamin D (commonly re-ferred to as "rickets" in children) is of unique historical value. Rickets was first de-scribed in the mid-1600s by Whistler and Glisson (Fraser and Scriver, 1979), but for decades thereafter, no progress was made in identifying the cause. Sir Edward Mellanby described the deficiency of a fat-soluble nu-trient as the cause for rickets (Mellanby, 1918). Then thereafter, Goldblatt and Soam-es (1923) demonstrated that skin exposed to sunlight or ultraviolet light produced a sub-stance with similar properties to this fat-soluble nutrient. This ultimately led to the discovery of the chemical structure of vita-min D (Windaus et al, 1936). Vitamin D and its metabolites have a significant clinical role because of their interrelationship with calcium homeostasis and bone metabolism. Rickets due to vitamin D deficiency is now rare except in populations with unusually low sun exposure and lack of vitamin D in fortified foods (Gordon et al, 2004). Sub-clinical vitamin D deficiency, as measured by low levels of 25OHD, has been described among adolescents (Das et al, 2006) and the elderly, and may contribute to development of osteoporosis and an increased risk of frac-tures and falls in elderly (Lips et al, 2006). Besides, its role in calcium and bone home-ostasis, vitamin D potentially regulates ma-ny other cellular functions (Holick, 2006).

Chemistry: Vitamin D, or calciferol, is a generic term and refers to a group of lipid soluble compounds with a four-ringed cho-lesterol backbone.

Sources: Two methods have been devel-oped for direct evaluation of the Vitamin D synthetic capacity of sunlight (and artificial UV sources). The first one uses an in vitro model of Vitamin D(3) synthesis (ethanol solution of 7-dehydrocholesterol, 7-DHC), and concentration of previtamin D(3) accu-mulated during an UV exposure is deter-mined using specially designed spectropho-tometric analysis. The second method utiliz-es photoisomerization of provitamin D in nematic liquid crystalline (LC) matrix, and visual estimation of accumulated previtamin D becomes possible due to special design of a LC cell (Terenetskaya, 2004).

Intestinal absorption is the other major source of vitamin D. As part of the diet, vit-amin D is found in fortified milk, fatty fish, and cod-liver oil and, to a lesser extent,

eggs. In the United States, milk fortified with vitamin D2 (ergocalciferol, a plant steroid) or vitamin D3 (cholecalciferol) is the principal source of dietary vitamin D. In other parts of the world, cereals and bread products were often fortified with vitamin D (Mansbach *et al*, 2009).

Absorption and metabolism: Dietary vitamin D is incorporated into micelles, absorbed by enterocytes, and then packaged into chylomicrons. Disorders associated with fat malabsorption, such as celiac disease, Crohn disease, pancreatic insufficiency, cystic fibrosis, and cholestatic liver disease, are associated with low serum 25-hydroxyvitamin D levels. Chylomicrons are transported to the liver via the portal circulation where vitamin D undergoes a hydroxylation process by 25-hydroxylase to form 25-hydroxyvitamin D (25OHD). Further hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (1,25OHD) occurs in the mitochondria of the proximal tubules of the kidney. 1,25OHD is the physiologically active form of vitamin D, with more than 25 metabolites identified, each with different biologic activities (Henry and Norman, 1974).

The synthesis of vitamin D and its metabolism to 1,25OHD is closely coupled to calcium homeostasis, and is modulated by parathyroid hormone, serum calcium, and phosphorus levels (Holick, 1989). When hypocalcemia occurs, serum PTH concentration increases and enhances tubular reabsorption of calcium, as well as the activity of alpha-1-hydroxylase in the kidney (Holick *et al*, 1995). This results in increased 1,25OHD production and, in turn, intestinal calcium absorption (Holick, 1994). PTH also stimulates bone osteoclast activity to mobilize bone calcium stores, thereby increasing serum calcium (Holick, 1996). Estrogen, placental growth hormone, and prolactin may also regulate vitamin D metabolism, playing a role during pregnancy to meet increased calcium demands (Kovacs and Kronenberg, 1997).

Metabolism of vitamin D: Vitamin D_3 is made in the skin from 7-dehydrocholesterol under the influence of UV light. Vitamin D_2 (ergocalciferol) is derived from the plant sterol ergosterol. Vitamin D is metabolized first to 25 hydroxyvitamin D (25OHD), then to the hormonal form 1,25-dihydroxyvitamin D (1,25(OH)$_2$D). CYP2R1 is the most important 25-hydro-xylase; CYP27B1 is the key 1-hydroxylase. Both 25OHD and 1,25(OH)$_2$D are catabolized by CYP24A1. 1,25(OH)$_2$D is the ligand for the vitamin D receptor (VDR), a transcription factor, binding to sites in the DNA called vitamin D response elements (VDREs). There are thousands of these binding sites regulating hundreds of genes in a cell-specific fashion. VDR-regulated transcription is dependent on comodulators, the profile of which is also cell specific. Analogs of 1,25(OH)$_2$D are being developed to target specific diseases with minimal side effects (Bikle, 2014).

Skeletal development and regulation of bone formation and resorption: Skeleton is a highly dynamic organ that constantly undergoes changes and regeneration. It consists of specialized bone cells, mineralized and unmineralized connective tissue matrix, and spaces that include the bone marrow cavity, vascular canals, canaliculi, and lacunae containing osteocytes. Bone also contains water, which represents at least 25% of its wet weight and provides much of its unique strength and resilience. Skeleton has structural and metabolic functions: Its structural function is critical for locomotion, respiration, and protection of internal organs. The structural connection between the skeleton and the hematopoietic system is particularly intimate; these two systems share both cells and local regulatory factors. Its metabolic function is largely as a storehouse for calcium, phosphorus, and carbonate and contributes to buffering changes in hydrogen ion concentration (Goltzman *et al,* 2015).

Deficiency and resistance: Vitamin D deficiency or resistance is caused by one of four mechanisms (Sahota, 2014): 1-Impaired availability of vitamin D, secondary to inad-

equate dietary vitamin D, fat malabsorptive disorders, and/or lack of photoisomerization. 2- Impaired hydroxylation by liver to produce 25-hydroxyvitamin D. 3- Impaired hydroxylation by kidneys to produce 1,25-dihydroxyvitamin D. & 4- End organ insensitivity to vitamin D metabolites; hereditary vitamin D resistant rickets (Misra *et al*, 2008).

Lack of vitamin D activity leads to reduced intestinal absorption of calcium and phosphorus. Early in vitamin D deficiency, hypophosphatemia is more marked than hypocalcemia. With persistent vitamin D deficiency, hypocalcemia occurs and causes the secondary hyperparathy-roidism that leads to phosphaturia, demineralization of bones and, when prolonged, to osteomalacia in adults and rickets in children. Muirhead *et al*. (1982) treated 23 patients with end-stage renal failure on maintenance haemodialysis with 1,25-dihydroxy vitamin D3 or 24-25-dihydroxy vitamin D3 for 3-32 months (total 232 patient months). They confirmed that 1,25-dihydroxy vitamin D3 was effective in controlling clinical, biochemical and histological features of renal osteodystrophy while 24,25-dihydroxy vitamin D3 did not have a useful therapeutic effect in the dose used. Hazzazi *et al*. (2013) studied the causes and clinical presentations of osteomalacia/rickets in adolescents, at the King Abdulaziz Medical City, Riyadh. They reported that osteomalacia was a significant health burden. They added that bone pain was the commonest symptom at diagnosis. Because of the high risk of osteomalacia associated with the use of anticonvulsants and steroids, it was advised that all patients on these drugs should be routinely screened for secondary osteomalacia. Wouters *et al*. (2015) in Europe stated that Rickets was a rare disease in developed countries, which affects growing bone. They reported two cases presenting with poor growth, severe pain, and respiratory problems secondary to calcipenic rickets. Munns *et al*. (2016) stated that vitamin D and calcium deficiencies are common worldwide, causing nutritional rickets and osteomalacia, which have a major impact on health, growth, and development of infants, children, and adolescents; the consequences can be lethal or can last into adulthood. They concluded that rickets, osteomalacia, and vitamin D and calcium deficiencies must be preventable global public health problems in the infants, children, and ado-lescents, and that implementation of international rickets prevention programs, including supplementation and food fortification, is urgently required.

Glucocorticoids, when used chronically in the high doses, inhibit intestinal vitamin D-dependent calcium absorption and therefore can cause osteomalacia. Guerreiro *et al*. (2007) reported that parathyroid hormone (PTH) and PTH-related protein (PTHrP) are factors sharing amino acid sequence homology and act via a common receptor. In tetrapods, PTH is the main endocrine factor acting in bone and kidney to regulate calcium and phosphate. PTHrP is an essential paracrine developmental factor present in many tissues and is involved in the regulation of ossification, mammary gland development, muscle relaxation, and other functions. Fish apparently lack an equivalent of the parathyroid gland and were long thought to be devoid of PTH. The existence of PTH-like peptides and their receptors in fish was firmed. Two forms of PTH, two of PTHrP, and a protein with intermediate characteristics designated PTH-L are encoded by separate genes in teleost fish. Three receptors encoded by separate genes in fish mediate PTH/PTHrP actions, whereas only two receptors have so far been found in terrestrial vertebrates. PTHrP has been more intensively studied than PTH, from lampreys to advanced teleost. It is expressed in many tissues with high concentration in fish blood. Administration of this peptide alters calcium metabolism and has marked effects on associated gene expression and enzyme activity in vivo and in vitro. This review provides a comprehensive overview of the physiological roles, distribution, and molecular rela-

tionships of the piscine PTH-like peptides. Gröber and Kisters (2012) reported that several drugs interfere with the vitamin D and bone metabolism. Drugs activate the pregnane X receptor disrupted vitamin D metabolism and vitamin D function. Also, medication oriented supplementation of the vitamin D ameliorated the pharmacologic action of some drugs, such as bisphosphonates, cytostatics and statins

Vitamin D stores decline with age, especially in the winter. Controlled trials have demonstrated that vitamin D and calcium supplementation can reduce the risk of falls and fractures in the elderly. Boucher (2912) reported that Loss of mobility or residential care restricts solar exposure. Reduced appetite and financial problems often add to these problems. Thus, hypovitaminosis D is common world-wide, but is more common and more severe in older people. Non-classical effects of vitamin D, depending on serum circulating 25-hydroxyvitamin D concentrations, are present in most non-bony tissues; disorders associated with hypovitaminosis D include increased risks of sepsis [bacterial, mycobacterial and viral], cardiovascular and metabolic disorders [e.g. hyperlipidemia, type 2 diabetes mellitus, acute vascular events, dementia, stroke and heart failure]. Many cancer risks are associated with vitamin D inadequacy, though causality is accepted only for colo-rectal cancer. Maintenance of repletion in healthy older people requires intakes of ≥ 800IU/day [20µg], as advised by the Institute of Medicine [IOM], but achieving such intakes usually requires supplementation. Excessive intakes are dangerous, especially in undiagnosed primary hyperparathyroidism or sarcoidosis, but the IOM finds doses <4000 IU/day are safe. Many experts suggest that $\geq 1000–2000$ IU (25–50µg) of vitamin D daily is necessary for older people, especially when independence was lost, or hypovitaminosis D could add to the clinical problem(s). Much higher doses than these are needed for treatment of established deficiency or insufficiency.

Calcium and vitamin D in osteoporosis: Sunyecz (2008) stated that osteoporosis poses a significant public health issue, causing significant morbidity and mortality. Calcium and vitamin D utilization in the optimization of bone health is often overlooked by patients and health care providers. In addition, the optimal standard of care for osteoporosis should encompass adequate calcium and vitamin D intake. Compliance to calcium and vitamin D therapy is paramount for effective prevention of osteoporotic fractures. A recently released algorithm (FRAX) estimating absolute fracture risk allows the health care provider to decide when pharmacologic therapy is warranted in addition to calcium and vitamin D. When pharmacologic therapy is advised, continued use of calcium and vitamin D is recommended for optimal fracture risk reduction.

Benefits of vitamin D repletion: Overt vitamin D deficiency, characterized by the hypocalcemia and/or hypophosphatemia and rickets and osteomalacia in children and osteomalacia in adults, is now uncommon in most developed countries. However, the subclinical vitamin D deficiency occurs even in developed countries associated with osteoporosis, increased risk of falls, and possibly fractures as well as aging (MacLaughlin and Holick, 1985). Vitamin D stores decline with age, especially in the winter (Tsai *et al*, 1987). In temperate areas such as Boston and Edmonton, for example, cutaneous production of vitamin D virtually ceases in winter (Webb *et al*, 1988). Thus, identification and treatment of vitamin D deficiency is important for musculoskeletal health and possibly even extraskeletal health, including the immune and cardiovascular systems. Generally, better vitamin D repletion may contribute to reducing chronic inflammatory problems such as periodontitis (Jabbar *et al*, 2011) and atheromatous disease, and might reduce acute vascular events due to arterial plaque disruption, inflammation being a major factor in atheromatous disease progression (Zhou *et al*, 1999). Tuberculosis infec-

tions were treated with sunshine and/or vitamin D before the anti-tuberculous drugs emerged. Sputum conversion rates fall with supplementation, but only in specific VDR genotypes (Martineau *et al*, 2011). Vitamin D status relates inversely to the circulating MMP9, a marker of atheromatous damage, which failed after supplementation (Timms *et al*, 2002). MMP9 formation in tuberculous lesions was suppressed by vitamin D (Coussens *et al*, 2009).

Wound healing, often slow in older ages, was enhanced experimentally by vitamin D (Tian *et al*, 1995). Hypovitaminosis D was associated with increased pressure sore risks in community dwellers in their 70s to 90s but not as an independent determinant since hypovitaminosis D was determined by existing co-morbidities (Kalav *et al*, 2011).

Clearly, adequate RCTs of supplementation are required to see whether causality can be demonstrated. Low baseline vitamin D status predicted reduced healing in the year after surgery for periodontitis, a common problem in older people, and giving vitamin D to subjects with severe periodontal problems improved post-operative bone defect resolution, supporting suggestions that the hypovitaminosis D may worsen periodontitis (Bashutski *et al*, 2011). Organ rejection risks after transplantation are reduced by vitamin D supplementation (Bitetto *et al*, 2010). If causality can be demonstrated for any or all of these suggestions by adequate RCTS of vitamin D supplementation, then provision of adequate vitamin D was used in these situations management (Holick, 2011)

Several studies have shown suboptimal serum levels of 25OHD and vitamin D intake in children in the United States and other countries (Cole *et al*, 2010).

Excess: In the 1940s and 1950s, a number of children developed hypercalcemia, sometimes associated with brain injury, thought to be a result of high concentrations of vitamin D in fortified milk products. Chronic intoxication may cause bone demineralization and pain. Vitamin D intoxication may occur in fad dieters who consume "megadoses" of supplements or in patients who take vitamin D replacement therapy for malabsorption, renal osteodystrophy, osteoporosis, or psoriasis (Gartner *et al*, 2005). Vitamin D intoxication was documented in adults taking more than 60,000 international units per day (Morgan and Weinsier, 1998). Keshtkar *et al*. (2015a) in Iran reported that few data on the efficacy of incremental doses of vitamin D from fortified foods among adolescents. They added that in developing countries an optimal model to fight vitamin D deficiency needs further research on bone health outcomes and the safety of vitamin D-fortified products. The modified version of this protocol could be applied in different parts of the country to assess the efficacy of a vitamin-D product. Symptoms of acute intoxication are due to hypercalcemia and include the confusion, polyuria, polydipsia, anorexia, vomiting, and muscle weakness. Keshtkar *et al*. (2015b) added that there must be a protocol, to be implemented with small modifications, can help policymakers in different parts of the world, particularly developing countries, and gather accurate information on the different aspects of bone health at the national level.

Requirements: The Institute of Medicine (IOM, 2010) released a report on dietary intake requirements for calcium and vitamin D. The dietary reference intakes were based upon the beneficial effects of calcium and vitamin D on skeletal health. The evidence supporting a benefit of vitamin D on extra skeletal outcomes was inconsistent, inconclusive as to causality, and insufficient, and therefore could not serve as a basis for dietary reference intake development (Ross *et al*, 2011). The intake at which the dose of vitamin D becomes toxic is not clear. The Institute of Medicine has defined the "tolerable upper intake level" (UL) for the vitamin D as 100micro-grams (4000 international units) daily for healthy adults and children 9 to 18 years. This is also the UL for pregnant and lactating women. The UL for infants

and children up to nine years old is lower (Tab. 2). Indications for high dose vitamin D supplementation and the UL for vitamin D supplementation are discussed in more detail separately

Estimates of vitamin D requirements vary, depend in part upon sun exposure and the standards used to define a deficient state. The Institute of Medicine (IOM, 2010) committee assumed minimal sun exposure when establishing the dietary reference intakes for vitamin D. The committee also concluded that a serum 25-hydroxyvitamin D concentration of 20ng/mL (50nmol/L) was sufficient for most individuals.

The Recommended Dietary Allowance (RDA) of vitamin D for children 1 to 18 years and adults through age 70 years is 600 international units (15mcg) with the RDA increasing to 800 international units (20-mcg) after age 71 (Tab. 2). For pregnant and lactating mothers, intake of 600 international units (15mcg) is recommended. However, some studies suggest that higher intakes may be necessary to maintain normal levels of 25OHD during the pregnancy and lactation (Hollis and Wagner, 2004a).

Vitamin D supplementation should be given to infants who are exclusively breast fed as vitamin D content of human milk is low. The Lawson Wilkins Pediatric Endocrine Society recommends supplementation with 400international units (units) daily of vitamin D beginning within days of birth for infants who are exclusively breast-fed. Most infant formulas contain at least 400 units/L of vitamin D, so formula-fed infants will also require supplementation to meet this goal unless they consume at least 1000 mL daily of formula. Vitamin D intake of at least 400units/day also recommended for children who do not consume at least one liter of vitamin D fortified milk daily (Hollis and Wagner, 2004b). Wagner et al. (2008) reported that rickets in infants attributable to inadequate vitamin D intake and decreased exposure to sunlight continues in the United States. There are also concerns for vitamin D deficiency in older children and adolescents. Because there are limited natural dietary sources of vitamin D and adequate sunshine exposure for the cutaneous synthesis of vitamin D is not easily determined for a given individual and may increase the risk of skin cancer, the recommendations to ensure adequate vitamin D status have been revised to include all infants, including those who are exclusively breastfed and older children and adolescents. It is now recommended that all infants and children, including adolescents, have a minimum daily intake of 400 IU of vitamin D must be after birth. The current recommendation replaces the previous recommendation of a minimum daily intake of 200 IU/day of vitamin D supplementation beginning in the first 2 months after birth and continuing through adolescence. They revised guidelines for vitamin D intake for healthy infants, children, and adolescents are based on evidence from new clinical trials and the historical precedence of safely giving 400 IU of vitamin D/day in the pediatric and adolescent population. New evidence supports a potential role for vitamin D in maintaining innate immunity and preventing diseases such as diabetes and cancer.

Casual exposure to sunlight gives amounts of vitamin D that are adequate to prevent rickets in many people, but is influenced by geographic location, season, use of sun block lotion, and skin pigmentation. As an example, a Caucasian infant's vitamin D requirements are met by exposure to sunlight for 30 minutes per week, clothed only in a diaper, or two hours per week fully clothed without hat (WHO, 2002). African-American individuals require approximately three-fold longer periods of sunlight exposure because of the protective pigmentation in their skin (Clemens et al, 1982). Currently recommended sun exposure for infants is insufficient to maintain vitamin D levels in the recommended range for dark-skinned infants and children, particularly at high latitudes and during the winter months. Brok et al. (2011) stated that The Danish Board of Hea-

lth recommended that: pregnant women are treated with a daily dose of vitamin D daily (10 micrograms); the emigrants with colored skin have their vitamin D level assessed during pregnancy; all children receive a daily dose of vitamin D (10 micrograms) until two years old. Despite of these recommendations two cases of the severe nutritional rickets among the emigrants children were discovered upon hospital admission. The symptoms were heterogeneous: delayed walking skills and convulsions. So, nutritional rickets is a tricky diagnosis, but is preventable.

Vitamin D requirements also may depend on disease states and concomitant medications. As an example, patients undergoing long-term treatment with steroids may benefit from higher levels of supplementation of vitamin D and calcium (De Sévaux *et al*, 2002). The best laboratory indicator of vitamin D adequacy is the serum 25-hydroxyvitamin D (25OHD) concentration. The lower limit of normal for 25OHD levels varies depending on the geographic location and sunlight exposure of the reference population (range 8-15 ng/mL). But, there was no consensus on the optimal 25OHD concentration for skeletal or extraskeletal health. The IOM (2010) suggested that a level of 20ng/mL (50nmol/L) is adequate. Vieth (1999) reported that for adults, the 5μg (200 IU) vitamin D recommended dietary allowance may prevent osteomalacia in absence of sunlight, but more needed to help prevent osteoporosis and secondary hyperparathyroidism. Other benefits of vitamin D supplementation were epidemiological implicated: Prevention of some cancers, osteoarthritis progression, multiple sclerosis, and hypertension. Total-body sun exposure easily provided equivalent of 250μg (10000 IU) vitamin D/d, suggesting a physiologic limit. Sailors in US submarines were deprived of environmentally acquired vitamin D equivalent to 20-50μg (800-2000 IU)/d. The assembled data from many vitamin D supplementation revealed a curve for vitamin D dose vs. serum 25-hydroxy-vitamin D 25(OH)D respo-

nse that was surprisingly flat up to 250μg (10000 IU) vitamin D/d. He added that to ensure serum 25(OH)D concentrations exceeded 100nmol/ L, a total vitamin D supply of 100μg (4000 IU)/d was required. Except in those with conditions causing hypersensitivity, without evidence of adverse effects with serum 25 (OH)D concentrations <140-nmol/L that require a total vitamin D supply of 250μg (10000 IU)/d to attain. Published cases of vitamin D toxicity with hypercalcemia, for which 25(OH)D concentration and vitamin D dose were known, all involve intake of ≥1000μg (40000 IU)/d. Because vitamin D is potentially toxic, intake of >25μg (1000 IU)/d was avoided even though the weight of evidence showed that the currently accepted, no observed adverse effect limit of 50μg (2000 IU)/d was too low by at least 5-fold. The serum parathyroid hormone (PTH) level typically is inversely related to 25-OH vitamin D levels in adults, and might be a useful secondary indicator of vitamin D insufficiency, which is weak for children.

Other Vitamin D input in some diseases:

Lung: better vitamin D status was associated with better lung function, independent of other factors including allergic status and in chronic pulmonary disease (CPD) though not in all cohorts. But, there could be an element of reverse causation in these associations since reduced exercise capacity may well reduce outdoor activity (Topannen *et al*, 2011).

Respiratory infection risk was high in renal failure but reduced in those on calcitriol (Tsujimoto *et al*, 2011). The new onset diabetes, hypertension and early cardiovascular death in patients on dialysis are major problems but replacement of vitamin D activity can reduce the risk of, or even correct glucose intolerance, reduce blood pressure and greatly reduce CVD mortality. However, this risk could increase if unduly high replacement doses were used, narrowing the therapeutically acceptable range of dosage of activated vitamin D (Tillis *et al*, 2011).

Vision: Vitamin D is postulated to protect

eyes from some common changes of ageing, including inflammation (Lee *et al*, 2012).

Chronic renal: Renal function falls with age and renal failure in older age is increasingly managed actively. Since renal activation of vitamin D is lost with extensive renal damage, renal osteodystrophy was a common and potentially severe bone disease for which activated vitamin D or its analogues are usually given as prophylaxis, together with measures for controlling serum calcium and phosphate concentrations. Respiratory infection risk was high in renal failure but reduced in those on calcitriol (Tsujimoto *et al*, 2011). New onset diabetes, hypertension and early cardiovascular death in patients on dialysis are major problems but replacement of vitamin D activity can reduce the risk of, or even correct glucose intolerance, reduce blood pressure and greatly reduce the CVD mortality (Tillis *et al*, 2011).

Ageing is associated with reduced peripheral arterial endothelium-dependent dilatation, probably due to increases in oxidative stress and reductions in locally synthesized nitric oxide. Whilst vascular endothelial function is adversely affected by lack of exercise, obesity, the menopause and other factors, and reduced in hypovitaminosis D (Seals *et al*, 2011) and was improved by supplementation (Ertek *et al*, 2012). Compliance (elasticity) of blood vessel walls falls with age and is associated with increases in blood pressure, as also seen with age.

Cancer: many cancers were more common in vitamin D deficiency and there is much convincing epidemiological and especially ecological evidence (Grant, 2012). But, only in colo-rectal cancer was available evidence accepted as demonstrating causality by bodies such as the International Agency for Research against Cancer (IARC, 2008).

Insect allergy: Keating *et al*. (2014) reported Vitamin D deficiency enhanced house dust mites induced influx of lymphocytes into BAL, ameliorated HDM-induced increased, and protected against the HDM-induced increase in baseline airway resistance. They

added that Vitamin D decreased inflammatory cytokine profiles in TH9 memory cells & CD4 (+) cells stimulated with HDM allergen, and was additive with dexamethasone in decreasing inflammatory cytokine production from T-cell subsets implicated in asthma. Vitamin D supplementation ameliorated atopic dermatitis severity as safe and tolerable therapy (Kim and Bae, 2016) as well as insect bites (Morsy, 2012) and Skeeter Syndrome (Abdel-Motagaly *et al*, 2017).

Information for patients: One must offer two types of patient education materials, "the basics" and "beyond the basics." The basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. One encourages the patient to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.).

Type 2 diabetes mellitus: Though there are strong associations of reductions in vitamin D status, but assessed, with increased risks of type 2 diabetes in many reported studies and in a few prospective studies were reported, very few randomized controlled trials were carried out to see whether correction of insufficiency can prevent T2DM diabetes. This is ongoing and will be published in due time by El-Tawdy *et al*. (In press)

Recommendations

Very few foods contain vitamin D; fatty fish and eggs are the exceptions. Dermal synthesis and foods fortified with vitamin D

are the major sources of the vitamin. Vitamin D3 (cholecalciferol) is synthesized non-enzymatically in skin from 7-dehydrocholesterol during exposure to the ultraviolet rays in sunlight. Cholecalciferol from the skin or diet must be 25-hydroxylated in the liver, then 1-hydroxylated in the kidneys to the active form, 1,25-dihydroxycholecalciferol (calcitriol) Vitamin D deficiency can be caused by unusually low sun exposure combined with lack of vitamin D fortified foods or malabsorption. Alternatively, impaired hydroxylation of vitamin D in liver or kidney can prevent metabolism into the physiologically active form. Rarely, genetic defects may cause the end organs to be unresponsive to vitamin D, as in hereditary vitamin D-resistant rickets (HVDRR). The Recommended Dietary Allowance for vitamin D is 600 international units (units) for adults through age 70 years and for children 1 to 18 years of age. For adults 71 years and older, 800 units (20 micrograms) daily is recommended for the prevention and treatment of osteoporosis. The excessive doses of vitamin D supplements in adults can result in intoxication. Acute intoxication symptoms are due to hypercalcemia; as confusion, polyuria, polydipsia, anorexia, vomiting, and muscle weakness. Long-term intoxication can cause bone demineralization, pain, and hypercalcemia in children, can cause brain injury.

The Institute of Medicine defined tolerable upper intake level (UL) for vitamin D as 100micrograms (4000 units) daily for the healthy adults and children 9-18 years. But, the UL for infants and children up to 9 years must be lower.

On the other hand, the supplementation of calcium and/or other nutrients should only be taken if medically indicated. These recommendations provided advice based on the available evidence but do not allow for the possibility that much higher doses may be more beneficial. But, adequate RCT data is not yet available for the potential benefits and risks of doses larger than 4000 IU/day over the long-term.

Table 1: Clinical symptoms of selected vitamin deficiencies

vitamin		Deficiency syndrome
Water-soluble vitamins		
Vitamin B1 (thiamine)	Thiamine pyrophosphate	Beriberi - congestive heart failure (wet beriberi), aphonia, peripheral neuropathy, Wernicke encephalopathy (nystagmus, opthalmoplegia, ataxia), confusion, or coma
Vitamin B2 (riboflavin)	Flavine adenine dinucleotide	Nonspecific symptoms including edema of mucus membranes, angular stomatitis, glossitis, and seborrheic dermatitis (eg, nose, scrotum)
Niacin (nicotinic acid)	Nicotinamide adenine dinucleotide	Pellagra - dermatitis on areas exposed to sunlight; diarrhea with vomiting, dysphagia, mouth inflammation (glossitis, angular stomatitis, cheilitis); headache, dementia, peripheral neuropathy, loss of memory, psychosis, delirium, catatonia
Vitamin B6 (pyroxidine, pyridoxal)	Transaminase cofactor	Anemia, weakness, insomnia, difficulty walking, nasolabial seborrheic dermatitis, cheilosis, stomatitis
Vitamin B12 (cobalamin)	One carbon transfer	Megaloblastic anemia (pernicious anemia). Peripheral neuropathy, with impaired proprioception, and slowed mentation.
Folate	One carbon transfer	Megaloblastic anemia
Biotin	Pyruvate carboxylase cofactor	Nonspecific symptoms including altered mental status, myalgia, dysesthesias, anorexia, maculosquamous dermatitis
Pantothenate	Coenzyme A	Nonspecific symptoms including paresthesias, dysesthesias ("burning feet"), anemia, gastrointestinal symptoms
Vitamin C (ascorbate)	Antioxidant, collagen synthesis	Scurvy - fatigue, petechiae, ecchymoses, bleeding gums, depression, dry skin, impaired wound healing
Fat-soluble vitamins		
Vitamin A (retinol, retinal, retinoic acid)	Vision, epithelial differentiation	Night blindness, xerophthalmia, keratomalacia, Bitot's spot, follicular hyperkeratosis
Vitamin D (cholecalciferol, ergocalciferol)	Prohormone for calcium regulation	Rickets, osteomalacia, craniotabes, rachitic rosary
Vitamin E (tocopherols)	Antioxidant	Sensory and motor neuropathy, ataxia, retinal degeneration, hemolytic anemia
Vitamin K (phylloquinone, menaquinone, menadione)	Clotting factors, bone proteins	Hemorrhagic disease

	Age	Micrograms daily	Micrograms daily	Adverse effects of excess
(calciferol) 1 mcg calciferol = 40 IU	Infants			Hypercalcemia, hypercalciuria, polydipsia, polyuria, confusion, anorexia, vomiting, bone demineralization
	0 to 12 months	10 (400 IU)	0 to 6 months: 25 (1000 IU)	
			6 to 12 months: 37.5 (1500 IU)	
	Children and adolescents			
	1 to 18 years	15 (600 IU)	1 to 3 years: 62.5 (2500 IU)	
			4 to 8 years: 75 (3000 IU)	
			9 to 18 years: 100 (4000 IU)	
	Males and females (including pregnancy and lactation)			
	19 to 50 years	15 (600 IU)	100 (4000 IU)	
	50 to 70 years	15	100	
	>70 years	20 (800 IU)	100	

Table 2: Vitamin D

References

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