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Journal of Parathyroid Disease

Journal of Parathyroid Disease 2016,4(1),20–24

Mini-Review

Vitamin D and its importance on public health

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Abstract

Vitamin D (a fat-soluble vitamin) is synthesized by humans and plants when they are placed under the influence of sunlight. Two major forms of vitamin D are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). People can get vitamin D2 from plants and vitamin D_3 from animal sources (mainly fatty fish). Most vitamin D is obtained through sunlight exposure. Vitamin D can also be received from fortified foods and dietary supplements made as medicine. Vitamin D deficiency (VDD) is an important public health problem because the low level of vitamin D in the blood is a risk factor for some severe diseases, such as cancer, heart disease, fractures and falls and etc. Vitamin D is also an important factor in the prevention and treatment of some skeletal and nonskeletal diseases. Skeletal diseases include rickets in children, osteoporosis, osteomalacia (known with bone pain) and bone loss in people with hyperparathyroidism. Nonskeletal diseases include high blood pressure and high cholesterol, diabetes, obesity, rheumatoid arthritis, multiple sclerosis, premenstrual syndrome (PMS), autoimmune diseases and cancers. Because there are many obstacles to sunshine exposure, including usage of sunscreen, hats, and other skin covers, decreased hours of sun exposure during aging and the winter; therefore, we can see a prompt increase in the number of people with VDD. Since the number of people with VDD is increasing, the research on this vitamin and its importance in public health and the prevention of severe diseases is very important. In this review, we summarize the association between VDD and some important diseases, and understand clinical benefits of vitamin D.

Keywords: Vitamin D, Osteoporosis, Osteomalacia, Ergocalciferol, Vitamin D deficiency, Malabsorption

Please cite this paper as: Borji S, Rafieian-Kopaei M. Vitamin D and its importance on public health. J Parathyr Dis. 2016;4(1):20-24.

Introduction

Vitamin D deficiency (VDD) is an important public health problem because the low level of vitamin D in the blood is a risk factor for some severe diseases, such as cancer, heart disease, fractures and falls etc. Vitamin D is also an important factor in the prevention and treatment of some skeletal and non-skeletal diseases (1,2).

Materials and Methods

For this review, we used a variety of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents such as vitamin D, osteoporosis, osteomalacia, ergocalciferol, vitamin D deficiency and malabsorption.

Biology and sources of vitamin D

Vitamin D (a fat-soluble vitamin) is synthesized by humans and plants when they are placed under the influence of sunlight. Two major forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D_3 (cholecalciferol). As both vitamin D_2 and vitamin D_3 need to be converted into the useful form (1,25[OH]2D), therefore those require go through two-step hydroxylation. The first hydroxylation is occured in the liver and the second hydroxylation is occured in the kidneys. 25(OH) D is made in liver and then it is converted into 1,25-dihydroxyvitamin D (1,25[OH]2D) in kidneys (1). While the blood level of 25-dihydroxyvitamin D is more than 1,25- dihydroxyvitamin D, but its efficiency is less than 1,25- dihydroxyvitamin D. The half-life of useful form of vitamin D (1,25[OH]2D), is about 15 hours, while the half-life of calcidiol (25-hydroxyvitamin D_3) is about 15 days. 1,25-dihydroxycholecalciferol (calcitriol), binds to vitamin D receptors (VDRs) that are located in many cells of the body, and then, its biological action will be started (2). Since vitamin D has an important role in blood regulation of phosphorous and calcium, therefore it can be useful for some conditions caused by low levels of phosphorous and calcium (3).

The most important and the easiest way that humans can obtain most of their vitamin D is the sunlight. Studies have demonstrated that people can get most of their vitamin D from 5-30 minutes of direct sunlight when the sun is high in the sky. Surprisingly, few commonly consumed foods naturally contain vitamin D, including oily fish such as salmon, mackerel and sardines and eggs (4). In Canada, Australia and the United States, adequate vitamin D is not achieved through dietary sources unless it is added to the food. Some foods such as milk, soy or rice beverage, yogurt, and cheese are fortified with vitamin D. Other sources include dietary supplements that contain vitamin D in various amounts including 400, 1000, 2000, 4000, 5000 and 50 000 IU vitamin D_3, multivitamins that contain 400

Received: 2 December 2015, Accepted: 1 January 2016, ePublished: 3 January 2016

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Implication for health policy/practice/research/medical education

Vitamin D deficiency is an important public health problem because the low level of vitamin D in the blood is a risk factor for some severe diseases, such as cancer, heart disease, fractures and falls etc. Vitamin D is also an important factor in the prevention and treatment of some skeletal and non-skeletal diseases. Skeletal diseases include rickets in children, osteoporosis, osteomalacia (known with bone pain) and bone loss in people with hyperparathyroidism. Non-skeletal diseases include high blood pressure and high cholesterol, diabetes, obesity, rheumatoid arthritis, multiple sclerosis, premenstrual syndrome (PMS), autoimmune diseases and cancers. Because there are many obstacles to sunshine exposure, including usage of sunscreen, hats, and other skin covers, decreased hours of sun exposure during aging and the winter; therefore, we can see a prompt increase in the number of people with vitamin D deficiency.

IU vitamin D. The most common form of vitamin D used for treatment is either vitamin D_2 or vitamin D_3. In some countries like Canada, Europe, Japan, and India, vitamin D_3 is used as a medicine and in the United States vitamin D_2 is used as a medicine (5).

Vitamin D deficiency; causes

The significant source of vitamin D for humans (children and adults) is disposal to sunlight. Therefore, anything that prevents penetration of sunlight into the skin can reduce vitamin D synthesis in the skin. For example, people who live in the northern half of the United States and Canada, are at high risk of VDD because they are living in a climate which do not prepare enough sunlight. VDD is also found in sunny climates for many reasons; including wearing a sunscreen reduces vitamin D_3 synthesis (6). Similarly, increased skin pigmentation will decrease the synthesis of vitamin D_3 in the skin. Thus, people with dark skins do not have ability to make adequate vitamin D in their skin. Since vitamin D is fat soluble, patients with fat malabsorption syndromes, are often unable to absorb vitamin D (include celiac disease, short bowel syndrome, and cystic fibrosis), and patients with nephritic syndrome lose 25(OH) D through excretion of vitamin D-binding protein in the urine (7). Some researchers in their studies show that levels of 25(OH) D have an inverse association with obesity, but have a direct association with age and lean body mass. Thus they express that people with a body mass index (BMI) of 30 or greater frequently have low blood levels of vitamin D (8). Some drugs and disorders which increase the catabolism of 25(OH) D and 1,25(OH)2D can make people at high risk for VDD. Drugs include some used to treat AIDS/HIV, dilantin, phenobarbital, and rifampin and disorders include chronic granuloma-forming, hyperparathyroidism and some lymphomas (9).

Vitamin D deficiency; groups at risk

Not getting enough sunlight

Since vitamin D is produced by the body when the sunlight hits the skin, adults in nursing homes or health care institutions, people who are living in northern latitudes (further away from the sun), wearing long robes or covering up for religious reasons and people who stay indoors for a long time are at a particularly high risk (6).

Limited diet

If you are suffering from milk allergies, or you are following a vegan diet, you are presumably at high risk of VDD. Because few foods contain vitamin D and most of the natural sources are animal-based, including oily fish such as salmon, mackerel and sardines, eggs and fortified powdered milk. A study from Japan demonstrated that limited exposure to sunlight and low vitamin D intake were causes amongst 31 confirmed cases of rickets (10).

Malabsorption disorders

Patients with fat malabsorption syndromes, such as Crohn disease, celiac disease, short bowel syndrome, and cystic fibrosis and people undergone resection of the small intestine are at high risk for this condition (7).

Infants and children who are fed with breast milk

Because of minimal amounts of vitamin D in human breast milk - the American Academy of Pediatrics recommended that all children require 200 IU vitamin D/d. Therefore this Academy recommended vitamin D supplementation starting at age 2 months for infants fed with breast milk (8).

Non-white ethnicity

Increased skin pigmentation reduces the skin's ability in absorbing UVB radiation. Therefore, vitamin D_3 synthesis decreases in response to sunlight exposure (8).

Elderly people (over 65 years)

As people age, various risk factors put them at high risk for VDD, including diminished dietary intake, spending lower time in the sun, decreased skin thickness, intestinal malabsorption (even if they take enough vitamin D), and impaired hydroxylation to convert vitamin D into its active form in the liver and kidneys (8).

Obesity

People with a BMI of 30 or greater often have a high prevalence of inadequate vitamin D levels (8).

Consequences of vitamin D deficiency

VDD prevents the absorption of consumed calcium and phosphorus from the intestinal wall. According many researches, there is an inverse relationship between levels of calcium and phosphorus and PTH. It has been observed an increased level PTH when the levels of calcium and phosphorus have been decreased. Increased levels of the PTH cause bone weakness and it also diminishes mineralization in the skeleton. In children, this defect results symptoms of skeletal deformities known as rickets (Rickets causes unusually deformity in bones). In adults will

exacerbate osteopenia and osteoporosis (patients usually complain of aches and pains in their joints and muscles) (7,11). VDD also contributes muscle weakness; affects adults have increasing body sway and falling, thereby increases the risk of fracture and affects children have trouble maintaining (11).

VDD is also associated with some serious diseases, including cardiovascular disease, cancer, sarcopenia, type 1 diabetes, multiple sclerosis (MS), osteoarthritis, cognitive dysfunction, depression, preeclampsia and more. One study demonstrated a high risk of increasing colorectal, breast, prostate, and many other cancers in individuals with lower 25 (OH) D intakes (12). Another study demonstrated that high intake of vitamin D to 1000 IU vitamin D_3/d would be linked with a diminished risk of colorectal and breast cancer as much as 50% (13).

Clinical benefits of vitamin D

Cancer: according results from many studies, there is a close association between high vitamin D levels and deminished risk of cancer. Some studies proved a higher risk of colon cancer and colonic adenomas in people with low levels of 25(OH) D in their blood (less than 30 ng/mL) compared to those with higher levels. Another study proved an inverse relationship between incidence of colon cancer and 25(OH) D levels less than 20 ng/mL (14). Some investigations demonstrated that women who spent more time in sunlight had significantly lower incidence rates of breast cancer, low progression of metastatic breast cancer and mortality rates of perimenopausal ovarian cancer. Some researchers suggested lower incidence of prostate cancer in those with high 25(OH) D levels (16 ng/mL or above) compared to those with low levels of 25(OH) D (below 16 ng/mL) (15).

Diabetes: both vitamin D and diabetes are pandemic. Nearly the number of 285 million people with diabetes is estimated in the world (7% of the world's population). This number is exceeding to 435 million. There is some evidence that VDD could contribute both type 1 and type 2 diabetes. Results from many studies demonstrated that measuring levels of vitamin D in blood caused decline in the risk of increasing type 2 diabetes (16). One study conducted by Zipitis et al showed diminished risk of increasing type 1 diabetes by 29% in children who took vitamin D supplements compared to children who did not take vitamin D supplements (17). An investigation suggested that children who are given 2000 IU of vitamin D per day in the first year of life are 80% less for risk of type 1 diabetes (18). Little vitamin D levels can also cause other autoimmune diseases such as rheumatoid arthritis, autoimmune thyroid disease, and MS.

Depression: results of many studies specify a correlation between vitamin D and the risk of developing depression. One cross-sectional investigation accomplished in Finland showed an inverse relationship between depression and vitamin D levels. People with high levels of vitamin D (above 22 ng/mL [56 nmol/L]) had a 35% lower risk of depression than people with low levels of vitamin D (below 14 ng/mL [34 nmol/L]) (19). A Japenies trial of pregnant women showed that those were taking 340 IU/d vitamin D_3 had half the risk of depression compared to those were taking 124 IU/d (20). Researchers during a study in Sweden observed lower vitamin D levels in those who tried suicide compared to healthy people (21).

Neurological problems: recently, studies showed association between inadequate vitamin D intake and development of Parkinson disease. More studies have also demonstrated links between low 25(OH) D levels (<25 nmol/L) and cognitive disorder compared to people with adequate levels (≥ 75 nmol/L) (22).

Hypertention: researchers demonstrated that high levels of vitamin D can decrease blood pressure in people with and without hypertension. During an experiment in 2012 in Denmark, some people with hypertension and some with low levels of vitamin D got 3000 IU daily for 5 months. The researchers showed decreased blood pressure in people getting vitamin D supplements and a higher reduction in blood pressures in people who had low levels of vitamin D (23). In another experiment in 2013 in Italy, one group of people with hypertension is taken 25 000 IU per week of vitamin D for 8 week. The researchers showed increased levels of vitamin D and decreased levels of blood pressure throughout the study (24).

Heart disease: many studies demonstrated the protective effect of vitamin D on the heart both directly (on the cells of the heart and blood-vessel walls) and indirectly (through the renin–angiotensin hormone system). In one study, patients with low vitamin D levels (<15 ng/mL) had higher risk (three times more) of hypertension than those with high levels (>30 ng/mL) (25). In another study, patients with less levels of vitamin D (<15 ng/mL) were 60% more possible to have heart disease compared to those with more levels (26).

Obesity: it is theorized that 25(OH) D levels have an inverse link with BMI and body fat but have a positive association with age, intake of vitamin D, and lean body mass. Weight loss is linked with an increase in levels of 25(OH) D among obeses (8).

Falls and fractures: many studies have demonstrated a link between high vitamin D levels and a decreased risk of falls and fractures in older adults. One study showed about 20% reduction of hip and nonspinal fractures in people who have given about 800 IU of vitamin D supplement per day. But this benefit has not been seen with about 400 IU vitamin D supplements per day (11).

Diagnostic procedure

The best blood factor for measuring vitamin D concentration in a person is 25(OH) D levels. Measuring of vitamin D level is not advised for all population, it is advised for those who are at high risk of VDD or insufficiency. Many different opinions are expressed on the levels of 25(OH) D that diagnose VDD. Some experts express levels of more than 30 ng/mL (75 nmol/L) as a normal level of vitamin D, levels of 20 to 30 ng/mL (50 to 75 nmol/L) as vitamin D insufficiency and 25(OH) D concentrations of less than 20

ng/mL (50 nmol/L) as VDD (27).

Treatment and prevention strategies

In general, it suggests that infants (0-1 year) need 2000 IU/d for 6 weeks or 50000 IU once weekly for 6 weeks to achieve blood level 25 (OH) D above 30 ng/ml. This therapy, should followed by maintenance therapy of 400-1000 IU/d. Children at age of 1-18 years need 2000 IU/d for at least 6 weeks or with 50000 IU for once a week to achieve blood level 25 (OH) D above 30 ng/ml. Followed by maintenance therapy of 400-1000 IU/d. Adults at age of 18 years and above need 50000 IU once a week for 8 weeks or its equivalent of 6000 IU/d for 8 weeks to achieve blood level 25 (OH) D above 30 ng/dl. Followed by maintain therapy of 1500-2000 IU/d. Patients with obesity malabsorption syndromes/on medications affecting vitamin D metabolism need 6000-10000 IU/d to maintain a 25 (OH) D level above 30 ng/ml. Followed by maintenance therapy of 3000-6000 IU/d. Many different types of vitamin D are used for the treatment of VDD or vitamin D insufficiency. The widely used forms of vitamin D are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Since vitamin D_3 may increase the level of vitamin D more effectively than vitamin D2, therefore it is suggested that vitamin D_3 is used for the treatment of VDD (27).

Conclusion

VDD is ceaselessly proliferating and these days it is a common problem among many people. Because of this, measuring of vitamin D level is advised for those who are at high risk of VDD or insufficiency. It also is recommended that people with VDD should be treated with vitamin D. More research is required to review the effect of both vitamin D_2 and D_3 on increasing the level of vitamin D individually and determine which type of vitamin (D_2 or D_3) is more effective on treatment of VDD.

Authors' contribution

SB prepared the primary draft and researched the data. Editing the final manuscript done by MRK.

Conflicts of interest

No to be declared.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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