FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol. 18, No 1, 2016, pp. 1–5 UDC 577.161.2:616-053.2

Invited Review Article

VITAMIN D SUPPLEMENTS – BENEFITS AND RISKS

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Abstract. *Vitamin D has several important functions including absorption of calcium and phosphorous, and facilitating normal immune system function. Sufficient amount of the vitamin is required for normal growth and development of bones and teeth, as well as improved resistance against certain diseases. There is growing evidence that there are huge benefits of vitamin D in promoting the human health, not only in infants for prevention of rickets but also effects on the immune system, blood pressure, reducing the risk of some cancers, prevention of diabetes mellitus type 1 trough stimulation of the pancreatic beta cells to secrete insulin. In contrast to these benefits certain patients genetically predisposed are at risk to develop a serious even fatal disease such as idiopathic infantile hypercalcemia. Withdrawal of vitamin D and reduction of calcium intake are lifesaving interventions for these babies. Recently it was found that recessive mutations in CYP24A1 gene are responsible for this disease. This gene encodes the enzyme 24 vitamin D hydroxylase which is important in the degradation metabolic pathway of the vitamin D. Although it was generally believed that idiopathic infantile hypercalcemia is the disease limited to infancy a number of studies yields that adults may have serious morbidity including nephrolithiasis, nephrocalcinosis, intermittent episodes of hypercalcemia leading to chronic kidney disease and in few cases to end stage renal disease. Therefore one should be very cautious in liberal prescribing vitamin D supplements and excessive exposure to sunlight, particularly in individuals with genetic predisposition*.

Key words: *vitamin D, supplements, CYP24A1, toxicity, children, nephrolithiasis, nephrocalcinosis*.

General

Vitamin D is called the "sunshine vitamin" because it's produced in the skin in response to sunlight. Vitamin D is a fat-soluble vitamin in a family of compounds that includes vitamins D1, D2, and D3. Vitamin D has several important functions including absorption of calcium and phosphorous, and facilitating normal immune system function. Sufficient amount of the vitamin is required for normal growth and development of bones and teeth, as well as improved resistance against certain diseases. The deficiency of vitamin D increases the risk of developing bone abnormalities such as osteomalacia or osteoporosis. It is believed that a 10 minutes a day of mid-day sun exposure is sufficient for production of adequate amount of vitamin D. Besides getting vitamin D through sunlight, it is provided through intake of certain foods and supplements [1]. Certain environmental factors and lifestyle influence the ability to get sufficient amounts of this vitamin through the sun alone such as pollution, use of sunscreen, spending more time indoors, long working hours in offices, living in big cities where buildings block sunlight. Therefore it is important to provide additional amounts of vitamin D from sources other than sunlight exposure. The recommended daily doses of vitamin D according to the Institute of Food and Agricultural Sciences (IFAS) [2] are:

- children and teens: 600 IU
- adults up to age 70: 600 IU
- adults over age 70: 800 IU
- pregnant or breastfeeding women: 600 IU

The consensus of scientific understanding appears to be that vitamin D deficiency is reached for serum 25-hydroxyvitamin D (25OHD) levels less than 20 ng/mL (50 nmol/L), insufficiency in the range from 20–32 ng/mL, and sufficiency in the range from 33–80 ng/mL, with normal in sunny countries 54–90 ng/mL, and excess greater than 100 ng/mL.

Health Benefits

There is growing evidence that there are huge benefits of vitamin D in promoting the human health, not only in infants for prevention of rickets but also effects on the immune system, blood pressure, prevention of diabetes mellitus type 1 trough stimulation of the pancreatic beta cells to secrete insulin.

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Received February 28th, 2016

Malignancies

Vitamin D has strong anticancerogenic effect for development of malignancies of the breast, colon, prostate, ovaries, esophagus, and lymphatic system. Several studies have shown that increased dietary intake of vitamin D as well as higher blood levels of vitamin D are associated with a reduced risk of colorectal cancer [3,4,5,6]. In experimental studies it has been found that vitamin D prevents the development of cancer trough enhancement of cellular differentiation, decreasing cancer cell growth, stimulating apoptosis and reducing tumor blood supply and angiogenesis [7,8,9,10]. Randomized The Women's Health Initiative study did not confirm the beneficial effect of vitamin D supplements for an average period of 7 years in reducing the incidence of colorectal cancer [11].

The limitation of majority studies which deal with the beneficial effects of vitamin D to human health arises from the fact that in dietary studies vitamin D produced in the skin from sunlight exposure is not taken in consideration. In most studies vitamin D level is measured in the blood at a single point in time and this may not correspond to a person's true vitamin D status. One may speculate that people with higher vitamin D intakes or blood levels have healthier behavior in general which reduces the cancer risk.

Upper respiratory tract infections

The beneficial effects of the vitamin D were questioned in the VIDARIS study reported in JAMA in 2012 [12]. In this randomized, double-blind, placebo-controlled trial adult participants were randomly assigned to receive an initial dose of 200,000 IU oral vitamin D3, then 200,000 IU 1 month later, then 100,000 IU monthly (n = 161) or placebo (n=161) for a total for 18 months,. The endpoints of this study were the number of upper respiratory tract infection episodes, their severity, duration and days off missed work. The results of this study were disappointing; no statistical significant difference was found in none of tested parameters.

Hypertension

In a meta-analysis performed by Kunutsor et al. [13] including a total of 283,537 participants, the investigators found that for each 10 ng/ml increase in someone's vitamin D levels, there was a 12% lower risk of developing hypertension. Also the people with the highest vitamin D levels had a 30% lower risk of developing hypertension compared to the people with the lowest levels. The limitation of this meta-analysis is that the analyzed studies were performed in United States and one may wonder if these results could be validated in other populations.

In another American study researchers found that that for every increase in vitamin D supplementation and vitamin D levels in the body, systolic blood pressure decreased but there was no changes in the diastolic blood pressure [14].

The researchers of the Women's Health Initiative Randomized Trial assigned women to either receive 1,000 mg per day of calcium plus 400 IU per day of vitamin D or a placebo pill. The results showed that there was no difference in blood pressure changes between the groups [15].

The study from Denmark investigated the effect of vitamin D supplements on lowering blood pressure in people with hypertension [16]. The study period was 20 weeks and the subjects were randomized to take 3,000 IU vitamin D per day D or placebo. This study showed that subjects in vitamin D group lowered their blood pressure more than those in the placebo group. The second conclusion was that subjects in the vitamin D group who had low levels of vitamin D at the beginning of the study had a bigger reduction in their blood pressures.

The limitation of abovementioned studies is that the hypertensive subjects were taking their medication during the study period, so it is uncertain if the lowering of the blood pressure was due to vitamin D or prescribed antihypertensive therapy.

Diabetes

There is evidence from experimental studies that vitamin D treatment improves glucose tolerance and insulin resistance and that supplementation with vitamin D restores insulin secretion in animals [17]. This is an indirect effect which is mediated by the flux of calcium trough the cell membranes; therefore low levels of extracellular calcium diminish insulin secretion. There are epidemiological studies which revealed greater incidence of type 1 diabetes related to geographic variation. The study from Finland analyzed 10,821 children who were supplemented with different vitamin D doses [18]. An important finding from this study was that children who took 2,000 IU of vitamin D daily had 80% lower risk to develop type 1 diabetes. Another point from this study was that vitamin D supplementation during the first year of life was critical for development of type 1 diabetes.

The evidence supports that maintaining adequate vitamin D status during pregnancy, nursing, infancy, and childhood may help prevent type 1 diabetes [19]. It is still the matter of controversy weather genetics of type 1 diabetes place individuals at risk for vitamin D deficiency or vice versa vitamin D deficiency increases the risk for type 1 diabetes. There are no studies to show the beneficial effect of vitamin D on the treatment of type 1 diabetes after diagnosis. Several studies have examined the impact of vitamin D supplementation on reversing type 1diabetes, and they have not been successful [17].

Risks

Cardiovascular risks

There is evidence that vitamin D deficiency is associated with cardiovascular morbidity and mortality, but also there is some evidence that high levels of vitamin D may also be associated with adverse arterial remodeling and poor outcomes [20,21]. It has long been known from case series that vitamin D excess can lead to atherosclerosis

and vascular calcification in humans. In NHANES III study there was a U-shaped relationship between vitamin D and mortality risk, particularly in women, with 25(OH)D levels >50 ng/L [22]. Although 1 meta-analysis that included 8 studies that assessed relatively high (>65 nmol/L) levels of 25(OH) found no significant change in risk of cardiovascular disease, another meta-analysis reported evidence of increased mortality with 25(OH)D concentrations >97.5 nmol/L [23].

Amer and Qayyum found that excessive vitamin D levels above 21 nanograms per milliliter were associated with an increase in CRP, which is known inflammatory marker and which is associated with the stiffening of blood vessels and a greater risk of developing cardiovascular problems [24].

One may have in mind that the role of vitamin D in the prevention and management of cardiovascular disease as well as the dose-response relationship of potentially harmful effects still remain to be established.

Idiopathic infantile hypercalcemia

There is pediatric entity entitled idiopathic infantile hypercalcemia (IIH) which presents in infants who may be severely ill with vomiting, poor appetite failure to thrive, seizures and if unrecognized and inappropriately treated may die. Biochemically these babies have hypercalcemia, hypercalciuria and suppressed parathormon. Imaging studies reveal bilateral nephrocalcinosis (Fig 1). Withdrawal of vitamin D and reduction of calcium intake are lifesaving interventions for these babies. The etiology was unknown until 2001 when Schlingmann and the group from Munster reported in The New England Journal of Medicine that homozygous *CYP24A1* mutations were cause for this disease in majority of babies [25]. This gene controls the enzyme 24hydroxylase which function is to degrade vitamin D and prevent sufficient synthesis of calcitriol. The authors wanted to validate their findings and therefore tested adult patients from former East Germany who had had signs of vitamin D toxicity as infants. The practice in East Germany was to administer parenterally 2 million units of vitamin D during the first 2 years of life. Indeed these adults carried homozygous mutations in *CYP24A1*.

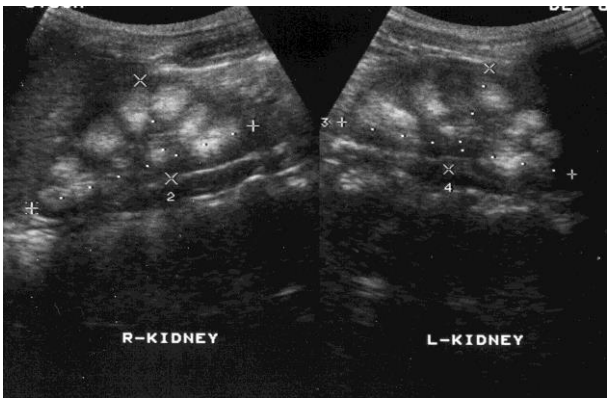

Fig. 1 Bilateral medullary nephrocalcinosis in a baby with idiopathic infantile hypercalcemia.

In Macedonia we have diagnosed on clinical basis 7 babies with IIH. We tested them for *CYP24A1* mutations and found that all had typical Central European E143del mutation. After the report in The New England Journal of Medicine there were additional reports in which *CYP24A1* mutations were found in adult subject with idiopathic calcium oxalate nephrolithiasis or unexplained nephrocalcinosis [26–33]. A study from Israel reported a small series of patients with nephrolithiasis/ nephrocalcinosis, even some of them progressed to terminal renal failure [33]. The etiology has not been established for decades and finally all were tested and found to carry *CYP24A1* mutations.

Recently in collaboration with Boston Children's Hospital (Harvard Medical School) using targeted next generations sequencing we diagnosed IIH in 12 year old girl who had incidental nephrocalcinosis [34]. She had normal growth and had not any problems as an infant. Along with this case and other study reports it is now clear that IIH is not the disease exclusively limited to infancy. This is important for these patients since they have to avoid lifelong vitamin D supplements and sunlight exposure. So it s questionable if IIH is a disease limited of infancy. The growing number of reports point that adult homozygous carriers of *CYP24A1* mutations may have serious morbidity – calcium oxalate nephrolithiasis, nephrocalcinosis, hypercalciuria, intermittent episodes of hypercalcemia. In the absence of hypercalcemia suppressed PTH may be clue to proper diagnosis.

Conclusion and Future Directions

Surely that vitamin D is very attractive for promotion overall human health. But one may have in mind that liberal administration of vitamin D supplements may have adverse effects in genetically susceptible individuals. Do we diagnose all patients with IIH? Is this only the tip of the iceberg? It seems that only patients with severe symptoms come to our medical attention. What can we do on the population basis? What is the prevalence of *CYP24A1* mutations in the Balkan populations? These questions remain to be answered in the near future. We can easily test for E143del. Family relatives will have great benefit of such testing. This is also very important for prenatal or early postnatal diagnosis of *CYP24A1* mutations carriers to implement early preventive measures.

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