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TOPICAL REVIEW

Vitamin D deficiency, atherosclerosis and cancer

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Abstract: Recently there has been intense interest to find if vitamin D deficiency may be related to cardiovascular disease, cancer and infection. Inadequate saturation with vitamin D may adversely affect immune and metabolic functions, causing non-skeletal medical disorders. Sunlight exposure induces vitamin D synthesis in the skin from a precursor, 7-dehydrocholesterol. Since the body produces vitamin D, this “vitamin” does not fulfill classical definition for a vitamin, being rather a prohormone. Vitamin D provided in the food has smaller role than the source synthesized in the skin. Vitamin D is hydroxylated in the liver into 25-OH-D. Because this product has a longer biological half life, it is the best indicator of body stores of vitamin D. Biologically active form is the next metabolite, 1-25 (OH)2 D. This product has a high binding affinity to a protein nuclear vitamin D receptor (VDR). Receptors for vitamin D have broad tissue distribution, including vascular smooth muscle, endothelium and even malignant cells. Deficiency of vitamin D in populations is high (30–60 % in the USA and Europe). This is particularly true about the northern latitudes where there are insufficient UV-B rays to promote the skin synthesis. In addition, there are campaigns to control sun exposure (fear of skin cancer), together with reduction in outdoor activities. No wonder that in aging people, in chronically ill and in subjects requiring long-term hospitalization, deficiency of vitamin D is very frequent and may adversely affect already compromised immunologic functions and resistance to infection *(Fig. 6, Ref. 43).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: vitamin D, vitamin D receptor, deficiency, heart disease, stroke, cancer.

Populations who live in the sun and who use limited clothing do not depend on vitamin D (D) intake in the food. Since most of D is generated in the human skin by UV light, it is more a prohormone, a substance that is a precursor to a hormone. Prohormones also include proinsulin and various precursors of D, D1 to D5 (1). These compounds can be defined as calciferols, because of their important role in calcium metabolism and promotion of favorable health outcomes (2). Calcemic effects of D have been known for over a century (rickets in poor children of London). The non-skeletal, metabolic effects of D have been subject of intensive research only in the last two decades. PubMed registered over 17,000 papers on D published in the past ten years. D isufficiency is clearly associated with suboptimal health. It appears that D is the nutrient of the decade.

The origin of active form of D and its mechanism of effect

Animal skin contains a substance similar to cholesterol: 7--dehydrocholesterol. Under the effect of UV light this molecule completely changes its structure. In order for 7-dehydrocholesterol to become the biologically active D (calcitriol), it has to acquire two hydroxyl groups, one in the liver the other one in the kidneys, thus becoming 1-25 dihydrocholecalciferol = 1-25 (OH)2 D (Fig. 1). Recently this activation process was also detected in the cells lining the respiratory tract. 1-25 (OH)2 D strongly reminds of the metabolic effect of steroid hormones, yet due to tradition we will use the term D.

After its final conversion in the kidneys the hormonally active form of D is released into the circulation bound to the globulin, with only a small fraction existing in free form. The free

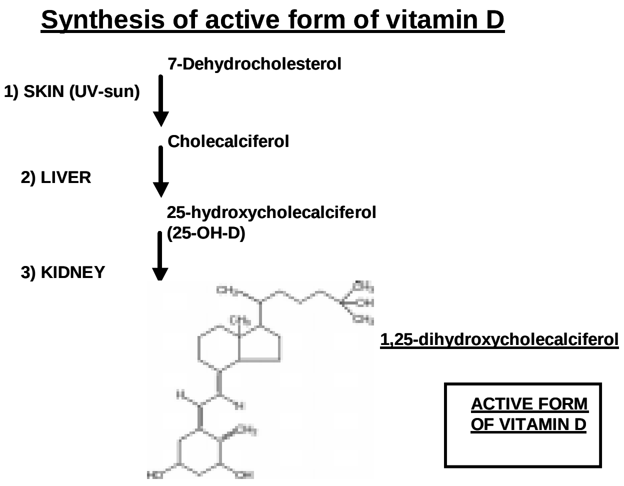

Fig. 1. A complex conversion of 7-dehydrocholesterol into active form of vitamin D takes place in the skin, in the liver and in the kidneys.

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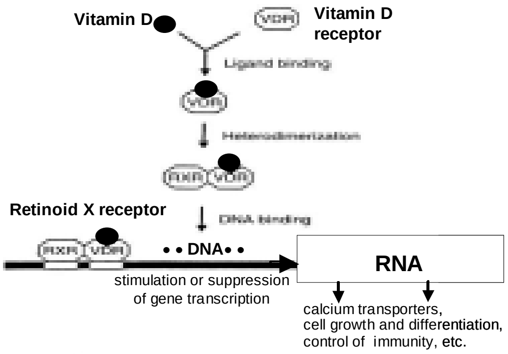
Coordinated effects of vitamin D and A receptors

Fig. 2. Transcriptional control of gene expression by vitamin D and retinoic acid receptors.

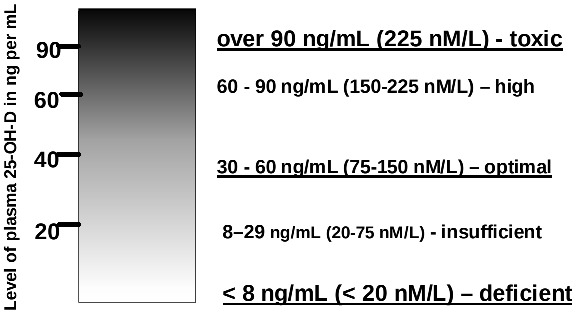
Vitamin D status: from deficiency to toxicity

Fig. 3. 25-OH-vitamin D concentration in blood serum is the best measure of vitamin D status.

form crosses the cell and nuclear membranes where it interacts with a vitamin D receptor (VDR). Many of the biological effects of D are mediated through this nuclear transcription (2,3). VDR in the nucleus of a cell encounters a retinoid X receptor (RXR) (Fig. 2). Remarkably, the precursor of RXR is retinoic acid derived from another fat soluble compound, vitamin A. Upon ligand binding with D the complex form of VDR undergoes a conformational change and forms a complex with a RXR. This binding results in an induction or repression of the specific mRNA, with the consequence of upturn or downturn of proteins responsible for the biologic effect of D. The VDR/RXR complex binds to specific sequences in target genes and may thus increase or decrease the rate of gene transcription.

Through this mechanism the vitamins, D and A may influence more than 200 genes. In the presence of D the VDR/RXR complex binds small sequences of DNA known as vitamin D response elements (VDREs) and initiates a cascade of molecular interactions that modulate the transcription of specific genes. This induces interaction of receptors with transcription factors resulting in stimulation of transport proteins which are involved in calcium metabolism.

The effect of D is much more extensive than the previously described basic function, i.e. the control of calcium metabolism. VDR belongs to the superfamily of steroid/ thyroid hormone receptors, present in almost all body systems, e.g. heart, brain, gonads, prostate and skin. Activation of VDR in the cells of the intestine, bone, kidney and parathyroid gland leads to regulation of calcium and phosphorus level in the blood and then to homeostasis of the skeletal system. The influence of D mediated through the VDR affects a wide range of metabolic functions, such as the immune system, cell proliferation and differentiation. Much of this is still in the domain of intensive research.

Epidemic of marginal vitamin D deficiency

Saturation of tissues with D is best reflected by the blood level of 25-OH-D (Fig. 3). This compound originates in the liver and it mirrors the synthesis of its precursor in the skin and the intake in food. 25-OH-D has a biological half life of several weeks. It is less accurate to measure the biologically active form, 1-25 (OH)2 D because of its short biological half life of only a few hours. The amount of D in food is expressed in two ways: a) in micrograms (ug) or, b) in international units (IU): 1 ug=40 IU. Most experts recommend daily food intake 800 - 1,000 IU, even higher intake in older age groups. The range for deficiency, optimum and toxicity has been under discusion. Most experts agree that latent deficiency of D is the blood level under 30 ng/mL (75 nmol/L) of 25-OH-D (4).

Several authors argue that the current recommended doses of D are inadequate to meet desirable serum levels of 25-OH-D. The daily intake in at least half of the US population should exceed 1,000 IU for the serum level to reach the desirable 30–60 ng/ml. However, the effect of food intake on serum level is not very predictable: it depends on the response of each individual. Daily intake of 6,400 IU increased serum 25-OH-D in pregnant women to 40 ng/mL but no further rise was noted.

Prevalence of vitamin D deficiency in the USA

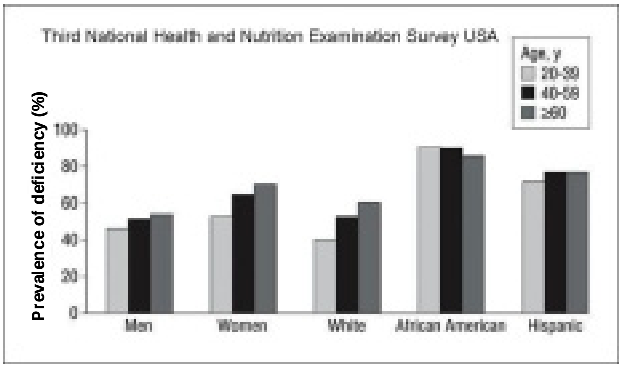

Fig. 4. Prevalence of insufficient 25-OH-vitamin D levels (<30 ng/mL) by sex and race/ethnicity across age groups in USA. Data from the Third National Health and Nutrition Examination Survey. According to Martins et al (4).

Important data on the prevalence of ViD deficiency in the USA was generated by the Third National and Nutrition Examination Survey (NHANES III). This included 7,186 male and 7,902 female adults 20 years of age and older (4–6), surveyed from 1988 to 1994. The prevalence of serum levels of 25-OH-D less than 30 ng/mL (<75 nmol/L) was higher in women, elderly persons, and racial/ethnic minorities (Fig. 4). Of the individual age and ethnic groups, lowest prevalence of D deficiency was observed in young white males aged 20–29. Women over 60 had high deficiency among all ethnic groups. Up to 70 % of older women were D deficient. The trend for deficiency manifests with advancing age. This has been consistently observed: biosynthesis of the active D slows down with aging. African Americans had the highest prevalence of deficiency, due to reflection of sunlight by the skin pigment. This extensive survey also explored D intake in food (5). Primary source of D were dairy products and fish. Food intake did not meet the recommended allowance. Lowest intake of D in food was found in female teenagers and in female adults.

A more recent report (7) complemented NHANES III by data from 13,369 participants in NHANES 2001–2004. Compared to NHANES III, the mean serum level of 25-OH-D further decreased to 24 ng/mL (from 30). The prevalence of 25-OH-D levels of less than 10 ng/mL increased to 6 % (from 2 %). The prevalence of serum levels of less than 10 ng/mL in non-Hispanic blacks increased to 29 % (from 9 %). Racial/ethnic disparities have persisted and they may have important implications for differences in general health.

There is a need for a critical review and revision of current recommendations for adult D intake (5–8). The most acceptable serum concentrations of 25-OH-D begin at 75 nmol/L (30 ng/mL), and the best range is from 90 to 100 nmol/L (36–40 ng/mL). In most persons, these concentrations could not be reached with the daily intake of 200 IU D for younger adults and 600 IU for older people. The American Academy of Pediatrics announced that it has doubled the amount of D recommended for infants, children and adolescents from 200 IU to 400 IU per day, starting in the first few days of life. For adults 800–1,000 IU per day was recommended.

In Europe, the Middle East and Asia D status highly differs among various countries. Within European countries, serum 25-OH-D is <25 nmol/L in 2–30 % of adults. Deficiency is increasing in the elderly and institutionalized to more than 80 % in some studies. A north-south gradient was observed for serum 25-OH-D with surprisingly higher levels in Scandinavia and lower levels in Italy and Spain and some Eastern European countries. This points to other determinants than sunshine, e.g. nutrition, food fortification and supplement use. Mean D intake in Scandinavia is 200–400 IU/d, twice that of other European countries. Very low serum 25-OH-D levels have been reported in the Middle East, e.g. Turkey, Lebanon, Jordan and Iran. In these countries serum 25-OH-D was lower in women than in men, probably related to clothing habits. In India, vitamin D deficiency was observed in more than 30 % of adult population. Risk groups are young children, the elderly and pregnant women (9).

Vitamin D deficiency and chronic diseases

Deficiency of D is associated with increased risk for multiple disorders. Traditionally, the role of D in calcium metabolism (rickets at young age, osteomalacia in adults) has long been acknowledged. Benefit of D for prevention of fractures has been widely reported (10). Antifracture efficacy increased significantly with higher preventive dose of D. This effect was dose dependent: higher dose appeared to reduce fractures by at least 20 % in individuals aged 65 or older.

This review focuses on lesser known role of D, namely its potential to benefit two universal mass killers, cardiovascular and neoplastic disease.

a) Cardiovascular system and vitamin D deficiency

A growing body of evidence suggests that D deficiency may adversely affect the cardiovascular system. It was previously documented in a cross-sectional population based study by Scandinavian authors (11) that serum levels of the active D were inversely related to blood pressure, to blood triglycerides and to triglyceride removal in an intravenous fat tolerance test. Serum levels of 25-OH-D correlated with fasting insulin, insulin sensitivity and lipoprotein lipase activity both in adipose tissue and in the skeletal muscle (11). These findings highlight the question for a role of D deficiency in a metabolic syndrome involving hypertension as well as hyperlipidemia and insulin resistance. Researchers have yet to determine the exact mechanisms connecting D deficiency with increased risk of cardiovascular disease. Studies have already shown that D can lower inflammation by increasing levels of anti-inflammatory messengers, like the cytokine interleukin 10. Association of D deficiency with cardiovascular disease can be found in a number of studies demonstrating a 30 % to 50 % higher cardiovascular morbidity and mortality with reduced sun exposure caused by changes in season or geographic latitude (12–17).

The year 2008 brought ten reports according to which the chronic deficiency of D is a risk factor for cardiovascular disease (3, 18–26). Low D status has been associated with the cardiovascular disease risk factors (hypertension, obesity, diabetes mellitus and the metabolic syndrome), as well as cardiovascular disease events including stroke and congestive heart failure (18). There is accumulating evidence that the D hormone exerts important physiological effects in cardiomyocytes, vascular smooth muscle cells and the vascular endothelium. Low levels of the 25-OH-D and D are associated with myocardial infarction, congestive heart failure, calcific aortic stenosis and deaths due to heart failure (19, 20). A prospective cohort study of 3,258 patients in duration of 7.7 years has shown that low 25-OH-D levels were significantly correlated with variables of inflammation (C-reactive protein and interleukin 6 levels), oxidative burden and cell adhesion. Low D status was associated with all-cause and cardiovascular mortality (21). A case-control study was conducted in 18,225 men in the Health Professionals Follow-Up Study. At the outset the men were aged 40 to 75 years and were free of diagnosed cardiovascular disease. During 10 years of fol-

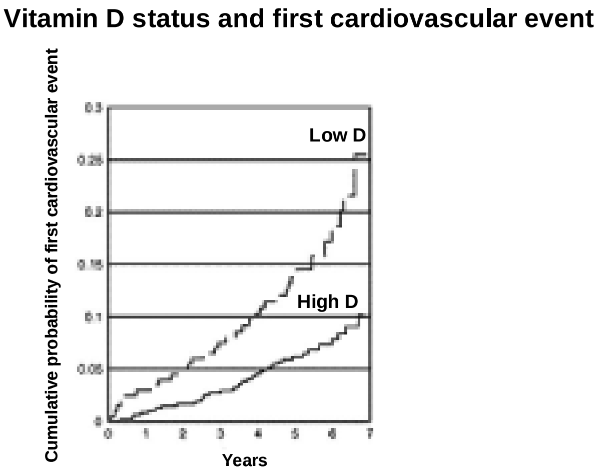

Fig. 5. Cumulative probability of first cardiovascular events in participants with low and high vitamin D status. The group with high status is represented by solid line, whereas the group with a low status is represented by dashed line. According to Wang et al (24).

low-up, 454 men developed nonfatal myocardial infarction or fatal coronary heart disease. Low D status was associated with higher risk of myocardial infarction in a graded manner, even after controlling for factors known to be associated with coronary artery disease (22). Treatment of D deficiency in otherwise healthy patients with 2,000–7,000 IU of D per day should be sufficient to maintain optimal D status (23). In the Framingham Offspring Study D deficiency was associated with incident cardiovascular disease (24). The cumulative probability of the first cardiovascular event was substantially higher in D-deficient hypertensive subjects (Fig. 5). A retrospective analysis of Australian database of deaths showed significant mortality increase in the winter. The largest increase in mortality rates was observed for heart disease. Winters in Australia are mild but winter increases of cardiovascular mortality are a significant problem. Increased blood pressure and lack of D in the winter are the most likely causes of such increase (25). A Cardiovascular Health (LURIC) study including 3,316 patients has shown that low D status was independently predictive for fatal strokes. Supplementation with D is a promising approach in the prevention of strokes (26).

A recent study (27) analyzed D deficiency and its significance in seriously ill patients in the intensive care unit. There was a high prevalence of hypovitaminosis D. All three patients who died from terminal disease had undetectable levels of 25-OH-D. Predicted mortality rates correlated with serum levels of D. The cause of hypovitaminosis D in critically ill is probably multifactorial. Possibly important is the limited exposure to sunshine during chronic illness. Another factor may be an altered D and parathyroid metabolism in critical disease. Increased mortality and D deficiency is an association and it appears difficult to establish causality between hypovitaminosis D and adverse outcomes. D has pleiotropic effects on immunity, endothelial and mucosal function, in addition to calcium and glucose metabolism. Deficiency of D may then worsen pre-existing immune and metabolic dysfunction.

b) Cancer and vitamin D

Human VDR is a key nuclear receptor exerting bioeffects that contribute to detoxication of exogenous and endogenous substrates and to cancer prevention (28). Most observational studies have associated increased D plus calcium intake with decreased risk of colorectal cancer (29–30). Blood samples from 25,260 subjects were used to investigate the relation of serum 25-OH-D with subsequent risk of getting cancer in the next eight years. Risk of colon cancer was reduced by 75 % in the third quintile (27–32 ng/ml) and by 80 % in the fourth quintile (33–41 ng/ml) of serum 25-OH-D (31). On the contrary, results of other authors do not provide support for wider acceptance of D supplementation to prevent colorectal cancer (32). Several case control and cohort studies support an inverse relation between D intake and breast cancer incidence (33–36), yet, other studies did not show such association (37). Dietary supplementation with D may be advisable for early stage of lung cancer (38). Numerous observational studies have found supplemental D to be associated with reduced risk of common cancers. Still, interventional studies to test such effect are lacking.

Recently, Lappe (39) performed a double-blind, randomized placebo controlled trial with all-cancer risk as an outcome. In multiple regression models, treatment with D and calcium, as well as serum 25-OH-D were significant and independent predictors of cancer risk (Fig. 6). Improvement of the calcium and D nutrition substantially reduced all-cancer risk in postmenopausal women. Calcium and D have been postulated to be anticancerogenic nutrients.

Studies in man regarding potential benefit of D have been corroborated in animal experiments. In a mouse model of die-

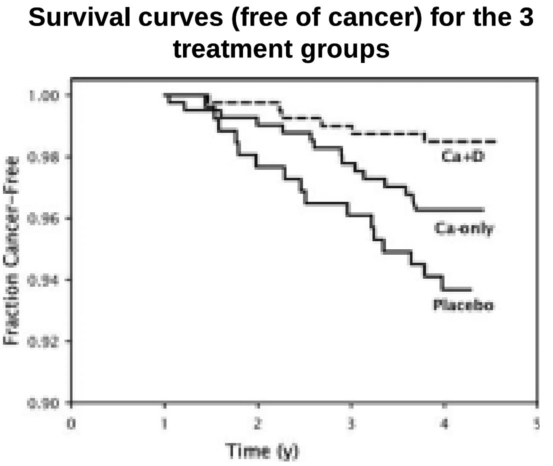

Fig. 6. Kaplan-Meier survival curves for the 3 treatment groups (placebo, Ca, vitamin D + Ca). The survival at the end of study for the Ca + D group is significantly higher than that for the placebo group. According to Lappe et al (39).

tary induction of colon cancer, colonic tumors were prevented by elevating dietary calcium and D to levels comparable with upper amount consumed by humans (40). Transgenic and knockout animals are powerful tools for identifying the molecular targets of bioactive food components. There is a need for increased use of these models to identify molecular targets for D.

The mechanism by which D may alter cancer development is still being delineated. At least 200 human genes contain D response elements. Many of these genes encode for proteins important in the regulation of cell proliferation, differentiation and apoptosis. When D saturation is suboptimal, these activities are impaired (41–43).

Vitamin D toxicity

Exposure to sunlight does not cause vitamin D toxicity. This is because within about 20 minutes of UV exposure the concentration of D precursors produced in the skin reaches an equilibrium, and any further D that is produced is degraded. Maximum endogenous production with full body exposure to sunlight is 250 ug (10,000 IU) per day.

Because synthesis of 1,25(OH)2D is tightly regulated, vitamin D toxicity usually occurs only if excessive doses ("megavitamin therapy") are taken. According to the US National Institutes of Health, the Upper Intake Levels (ULs) for vitamin D are for one year of age or older: 50 micrograms (2,000 IU).

The main symptoms of D toxicity result from hypercalcemia: anorexia, nausea, and vomiting, often followed by polyuria, polydipsia, weakness, and eventually renal failure.

Conclusion

Prevalence of D deficiency is very high (30–60 % of the US and European population). Metabolic role of D is more extensive than the traditional function in regulating the calcium metabolism. VDR belongs to the superfamily of steroid/thyroid hormone receptors that are present in most tissues, e.g. heart, brain, gonads, prostate, skin and also in cancer cells. The influence of D mediated by VDR affects a wide range of metabolic activities including immunity, cell proliferation, apoptosis and cell differentiation. Active research in this field promises new insights on possible cancer chemoprevention and chemotherapy.

Deficiency of D is associated with increased cardiovascular risk, above and beyond established cardiovascular risk factors. The higher risk associated with D deficiency was particularly evident among individuals with high blood pressure. This deficiency is easy to screen for and easy to treat with supplementation. Larger observational studies and randomized clinical trials are needed to determine whether D supplementation could have any potential benefit in reducing cardiovascular disease events and mortality risk.

In evaluating the data, association should be strictly differentiated from causality. This applies especially to old and chronically ill where the disease preexisted before decreased food intake and an insufficient exposure to sunlight. Epidemiology with geographic medicine should evaluate the associations between sunlight exposure and cardiovascular/ neoplastic risk related to geographic latitude and in populations with increased skin pigmentation. Concern about skin cancer is confronted with an interesting dilemma: the essential function of the "sunshine vitamin" versus cancerophobia promoting "less fun in the sun".

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