Vitamin D: ultraviolet light and well-being of older people

Veleva, B.I.

Chapter 1

General introduction

VITAMIN D SYNTHESIS AND VITAMIN D RECEPTORS

Vitamin D is a hormone produced in the skin from 7-dehydrocholesterol (provitamin D) via a non-enzymatic process involving ultraviolet light. The product of this photolysis, previtamin D, undergoes further hydroxylation in the liver to 25-hydroxyvitamin D (25(OH) D_3, calcidiol) by 25-hydroxylase and is converted in the kidney to the biologically active form 1,25-dihydroxyvitamin D_3 (1,25 $(OH)_2$ D_3, calcitriol) through a second hydroxylation by 1-alpha hydroxylase. Recent genome-wide association studies have identified several variants near genes involved in cholesterol synthesis (DHCR7), hydroxylation (CYP2R1, CYP27B1, CYP24A1) and vitamin D transport (GC, vitamin D binding protein) that influence vitamin D status. Genetic variation in these loci can cause vitamin D insufficiency and disease [1,2].

1,25-dihydroxyvitamin D_3 has multiple functions in the regulation of calcium and phosphorus metabolism, immune and cardiovascular systems, skin, muscle function, cellular growth control and possibly numerous other biological processes [3]. These biological activities are mediated by the vitamin D receptor, a nuclear receptor protein which functions to control the expression of genes in a cell-selective manner [1,4]. Most cells and organs in the human body have vitamin D receptors [4-7].

VITAMIN D SIGNALLING AND TARGET ORGANS/ CELLS: DOES VITAMIN D PLAY AN ESSENTIAL ROLE IN BIOLOGICAL PROCESSES OR IN CURING DISEASE?

Observational studies have described inverse associations between vitamin D status and a large number of diseases and health risks such as osteoporosis, fracture risk, fall risk, cardiovascular diseases, malignancies, infections, and autoimmune diseases [8-12]. Recently, a large number of randomised controlled trials (RCTs), meta-analyses of RCT's and Mendelian randomisation studies have investigated causality concerning vitamin D levels and diseases.

VITAMIN D AND BONE MINERAL HOMEOSTASIS

One of the principal functions of vitamin D is to promote calcium absorption from the intestine and maintain calcium homeostasis in the body. Patients with functional mutations in 25-hydroxylase (CYP2R1) develop vitamin D-dependent rickets and respond to physiological doses of calcidiol [13]. Patients with functional mutations in 1-alpha hydroxylase (CYP27B1) develop skeletal defects or classic rickets, muscle weakness and growth retardation, all of which

can be cured with physiological levels of calcitriol [14]. Vitamin D and calcium are substrates in a multifactorial process that maintains bone homeostasis. The multifactorial nature of this process makes it difficult to determine the threshold level of vitamin D at which the balance becomes negative and triggers disease: insufficient mineralisation of the matrix leads to the development of osteopenia or osteoporosis. RCTs and meta-analyses of vitamin D trials show no negative effects on bone density or fracture risk when the baseline level of 25-hydroxyvitamin D is higher than 40 nmol/l [15-19]. Furthermore, a study assessing the genetic and clinical determinants of fracture risk, including genome wide associations and Mendelian randomisation, showed an effect of bone mineral density on fracture risk but no causality regarding vitamin D levels [20]. However, this study was carried out in a healthy population and did not consider the possibility of a threshold-dependent relation to the risk of fractures and vitamin D levels.

VITAMIN D AND FALLS

Vitamin D receptors have also been identified in muscles, where 1,25 $(OH)_2$ D_3 influences calcium uptake and controls protein synthesis in the fast twitch muscle fibres that maintain balance and prevent falls [21]. Reversible muscle atrophy has been observed in individuals with vitamin D deficiency [22]. The RCTs and meta-analyses carried out to examine the effect of vitamin D supplementation in the prevention of falls are inconclusive but do delineate two aspects: vitamin D supplementation is effective in doses 700-1000IU [23] and in people with a low vitamin serum concentration [24]. A recent, large RCT by Scragg et al. that included 5110 participants and an intervention consisting of vitamin D supplementation in monthly doses of 100,000 IE for 3.3 years showed no beneficial effects of vitamin D on the prevention of falls. However, the study population had a mean baseline deseasonalized 25(OH)D concentration of 66 nmol/l and only 25% of the subjects had 25(OH)D levels below 50 nmol/l.

Clinical trials with very high vitamin D supplementation levels of 60,000 IE monthly or 500,000 IU annually showed a counterproductive effect and actually increased the risk of falling [25,26].

VITAMIN D AND CANCER

Preclinical studies have demonstrated that vitamin D can modulate anticancer activities such as antiproliferation, countering in sensitivity to antigrowing signal and evasion of apoptosis [27]. Vitamin D receptor signalling enhances adhesion and suppresses invasive potential [28], as well as playing a role in maintaining genomic integrity and facilitating DNA repair [29]. The effects of vitamin D supplementation on the risk of cancer were discussed in a systematic review of

meta-analyses, which concluded that the studies analysed provided no evidence supporting a causal relationship between low vitamin D levels and cancer [30]. However, the authors of the systematic review noted that people with low vitamin D levels were underrepresented in the RCTs included in the meta-analysis and that studies of longer duration have suggested a beneficial effect of vitamin D supplementation [31,32].

VITAMIN D AND RISK OF HYPERTENSION

Vitamin D corrects abnormalities in calcium homeostasis and regulates the renin-angiotensin system, both of which play a role in the development of hypertension [33,34]. Meta-analyses on the effect of vitamin D supplementation on blood pressure have caused controversy. Two large meta-analyses took into account the effect of supplementation on subgroups with very low baseline 25(OH)D levels: the first study found no effect of vitamin D on blood pressure [35], while the second study found a lower diastolic blood pressure in hypertensive patients with very low baseline 25(OH)D levels [36]. The VIDA study, which recruited 5110 participants, reported a beneficial effect on arterial function in participants with low 25(OH)D levels following supplementation with high monthly doses of vitamin D [37]. Furthermore, a Mendelian randomised trial investigated whether genetic variants that affect circulating concentrations of 25(OH)D also affect blood pressure and risk of hypertension [38]. In phenotypic analyses (N=49,363), an increased 25(OH)D concentration was associated with decreased systolic blood pressure and reduced odds of hypertension.

VITAMIN D AND IMMUNE SYSTEM

1,25 $(OH)_2$ D_3 has a wide range of immunomodulatory effects in innate and adaptive immune cells [39]. Inflammatory immune signals can stimulate the expression of CYP27B1, allowing macrophages to locally produce 1,25 $(OH)_2$ D_3 [40,41]. Active metabolites of vitamin D then enhance the antimicrobial activity of macrophages, allow dendritic cells to become adherent, diminish the secretion of proinflammatory cytokines and enhance secretion of IL-10 (interleukin 10, an anti-inflammatory cytokine) and TNF-alpha (tumour necrosis factor alpha), which modulates T-cell behaviour through effects on antigen presenting cells and cell phenotype and function [39]. High-dose vitamin D supplementation in patients with multiple sclerosis produced pleotropic immunomodulatory effects that included reduction of interleukin 17 levels (IL-17). IL-17 production damages the blood-brain barrier, facilitating the entry of immune cells into the central nervous system [42]. A systematic review and meta-analysis of individual participant's data (11,321 participants) showed that vitamin D supplementation may reduce acute respiratory infections, especially in people with vitamin D deficiency [43]. A retrospective, observational

analysis of 190,000 participants that aimed to determine if circulating 25(OH)D levels are associated with SARS-CoV-2 positivity rates reported that participants with vitamin D serum levels lower than 50 mmol/l had a 54% higher positivity rate compared to those with serum levels of 75-85 nmol/l/ [44].

EFFECTS OF SUN/ULTRAVIOLET LIGHT ON HUMAN HEALTH

The most well-known effect of sun and ultraviolet light on human health is the synthesis of vitamin D in the skin, but other effects have also been described. There is growing evidence that harm due to avoidance of sun exposure might actually outweigh the risks of skin cancer, and that a satisfactory balance is possible [45]. Interestingly, while sunburns appear to double the risk of melanoma, non-burning sun exposure is associated with a reduced risk of melanoma [46]. Furthermore, observational studies have described inverse associations between sun radiation and several cancers such as non-Hodgkin lymphoma and colorectal, breast and prostate cancer [9]. Well described positive effects of sunlight include the prevention and treatment of skin diseases like psoriasis, eczema, vitiligo and acne [47,48].

Epidemiological studies have shown that blood pressure correlates with geographical latitude [49] and that sunlight exposure might reduce both blood pressure and CVD [50,51]. In a competing risk scenario study of 29,518 Swedish women with prospective 20-year follow-up (Melanoma in Southern Sweden cohort), Lindqvist et al. showed that longer life expectancy among women with active sun exposure habits was related to a decrease in CVD and non-cancer/non-CVD mortality [50]. The skin has the potential to contribute to cardiovascular homeostasis by increasing the circulating nitric oxide (NO) metabolite pool. Laboratory studies investigating the effect of ultraviolet light type A on blood pressure demonstrated that both skin and dermal vasculature contain biologically significant stores of nitric oxide (NO) that can be directly mobilized by UV type A radiation [52,53]. NO is a key vasoprotective molecule canonically produced in the cardiovascular system. It is an important determinant of peripheral vascular resistance and blood pressure, as well as being associated with vasorelaxation, anti-atherogenic and anti-platelet phenotypes [54].

A mood-enhancing and hence quality of life enhancing effect of ultraviolet light has also been reported [55-58]. Modulation of mood triggered by ultraviolet light is possibly mediated through the skin and may involve three local systems: i) the skin analog of the hypothalamic-pituitary-adrenal (HPA) axis [59], ii) the serotoninergic/melatoninergic system [60], and iii) the immune system [61,62]. These pathways are assumed to inteact with systemic mechanisms of body homeostasis [61].

VITAMIN D, SUNLIGHT AND OLDER PEOPLE

With ageing, the production of vitamin D in the skin declines [63]. This is the combined effect of a decline in the ability of the kidney to synthesize $1,25(OH)_2D_3$ and an increase in catabolism of $1,25(OH)_2D_3$ by CYP24A1, which contributes to age-related bone loss [2]. Aging is also associated with a decrease in the concentration of the vitamin D receptor [2]. Vitamin D deficiency (serum 25(OH)D3 < 30 nmol/l) and insufficiency (serum 25(OH)D3 > 30 nmol/l<50 nmol/l) is common in older people, and is mediated by factors such as a reduction in mobility, greater time spent indoors, a lower intrinsic skin response to UV radiation and a reduced dietary vitamin D intake [64]. Almost all nursing home residents are vitamin D insufficient if vitamin D is not supplemented [65,66].

The Dutch Health Council (2012) advises standard daily vitamin D supplementation of 800 IU (20 mcg) for persons aged ≥ 70 years, with a target 25(OH)D serum concentration of ≥ 50 nmol/l [67]. This recommendation is in line with advice from the Institute of Medicine (IOM) (2011) [68,69] and the Expert Working Group on vitamin D (2012) [70]. While these guidelines are clear and easy to apply, a number of issues remain. The guidelines are possibly too general for a heterogeneous population of people aged 70 years and over, as this group often includes both the fit and active and the very frail. Is the recommended level of vitamin D supplementation appropriate for everyone in this heterogeneous group? Levels of 25(OH)D are known to be influenced by age [64], body mass index [71], medication use [67] and comorbidities [72]. How the medical doctors taking care of this population follow the guidelines, do they meet difficulties and what are they? And if there is good compliance to the guidelines, how do doctors regard sun exposure in the older population? Are they happy with vitamin D supplementation alone, assuming that it is the only significant effect of sun exposure? And once an adequate vitamin D level is achieved, do they feel that avoidance of sun exposure amounts to avoidance of its deleterious effects? The latter topic is quite controversial even in scientific literature. As already mentioned in the introduction, there is growing evidence that sun exposure may have positive effects on human health via mechanisms other than vitamin D synthesis alone, possibly providing protection against cancer, cardiovascular disease and autoimmune disease. It might also positively influence mood, depressive disorders and well-being. These data are predominantly derived from observational studies. A small number of RCTs have been conducted but using only small samples and with inconclusive findings. We formulated the goals of our study to specifically address these questions.

AIMS OF THIS THESIS

The overall aim of the studies described in this thesis was to investigate vitamin D supplementation strategies in older people and nursing home residents in the Netherlands, and to explore possible beneficial effects of ultraviolet light, over and above vitamin D synthesis, on the well-being and quality of life of nursing home residents with dementia. The detailed objectives of these studies:

Chapter 2 presents an observational study designed to investigate the efficacy of recommended dietary vitamin D supplementation in a population of frail nursing home residents. We investigated whether a sufficient serum 25(OH)D3 level was reached to ensure expected skeletal and non-skeletal effects.

Chapter 3 examines the vitamin D prescribing behaviour of elderly care physicians (ECPs) and general practitioners (GPs) in the Netherlands among people aged 70 years and over. We discuss controversial topics concerning vitamin D supplementation with the aim to clarifying and promoting vitamin D supplementation in older age groups.

Chapter 4 is a systematic review exploring and summarizing evidence obtained from clinical trials and observational studies on the effects of ultraviolet light. We discuss the effects of ultraviolet light applied to the skin or as a component of light therapy applied to the eyes, considering the impact on mood, depressive disorders and wellbeing.

Chapter 5 describes a randomized controlled trail that compared the effect of ultraviolet light to oral vitamin D supplementation on the well-being and quality of life of nursing home residents with advanced dementia.

Chapter 6 considers the impact of vitamin D supplementation and ultraviolet radiation on blood pressure changes in nursing home residents with dementia.

Chapter 7 is a general discussion of the main results of the studies, considers the clinical implications of our findings for the daily practice of physicians working with older people, and makes some recommendations for future research.

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