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

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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.

REFERENCES

1. Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet.* 2010;376(9736):180-188.
2. Christakos S, Li S, De La Cruz J, Bikle DD. New developments in our understanding of vitamin metabolism, action and treatment. *Metabolism.* 2019;98:112-120.
3. Pike JW, Christakos S. Biology and Mechanisms of Action of the Vitamin D Hormone. *Endocrinol Metab Clin North Am.* 2017;46(4):815-843.
4. Meyer MB, Goetsch PD, Pike JW. Genome-wide analysis of the VDR/RXR cistrome in osteoblast cells provides new mechanistic insight into the actions of the vitamin D hormone. *J Steroid Biochem Mol Biol.* 2010;121(1-2):136-141.
5. Wacker M, Holick MF. Vitamin D - effects on skeletal and extraskeletal health and the need for supplementation. *Nutrients.* 2013;5(1):111-148.
6. Rosen CJ, Adams JS, Bikle DD, et al. The nonskeletal effects of vitamin D: an Endocrine Society scientific statement. *Endocr Rev.* 2012;33(3):456-492.
7. Holick MF. Vitamin D: extraskeletal health. *Endocrinol Metab Clin North Am.* 2010;39(2):381-400, table of contents.
8. van Schoor NM, Lips P. Worldwide vitamin D status. *Best Pract Res Clin Endocrinol Metab.* 2011;25(4):671-680.
9. van der Rhee H, Coebergh JW, de Vries E. Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies. *Eur J Cancer.* 2013;49(6):1422-1436.
10. Forman JP, Giovannucci E, Holmes MD, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension.* 2007;49(5):1063-1069.
11. Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. *Hypertension.* 2008;52(5):828-832.
12. Antico A, Tozzoli R, Giavarina D, Tonutti E, Bizzaro N. Hypovitaminosis D as predisposing factor for atrophic type A gastritis: a case-control study and review of the literature on the interaction of Vitamin D with the immune system. *Clin Rev Allergy Immunol.* 2012;42(3):355-364.
13. Molin A, Wiedemann A, Demers N, et al. Vitamin D-Dependent Rickets Type 1B (25-Hydroxylase Deficiency): A Rare Condition or a Misdiagnosed Condition? *J Bone Miner Res.* 2017;32(9):1893-1899.
14. Fraser D, Kooh SW, Kind HP, Holick MF, Tanaka Y, DeLuca HF. Pathogenesis of hereditary vitamin-D-dependent rickets. An inborn error of vitamin D metabolism involving defective conversion of 25-hydroxyvitamin D to 1 alpha,25-dihydroxyvitamin D. *N Engl J Med.* 1973;289(16):817-822.
15. Reid IR. Vitamin D Effect on Bone Mineral Density and Fractures. *Endocrinol Metab Clin North Am.* 2017;46(4):935-945.
16. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Engl J Med.* 1992;327(23):1637-1642.
17. Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes--authors' reply. *Lancet Diabetes Endocrinol.* 2014;2(5):364-365.
18. Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med.* 2012;367(1):40-49.
19. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *Cochrane Database Syst Rev.* 2014(4):CD000227.
20. Trajanoska K, Morris JA, Oei L, et al. Assessment of the genetic and clinical determinants of fracture risk: genome wide association and mendelian randomisation study. *BMJ.* 2018;362:k3225.

21. Dhaliwal R, Aloia JF. Effect of Vitamin D on Falls and Physical Performance. *Endocrinol Metab Clin North Am.* 2017;46(4):919-933.
22. Ziambaras K, Dagogo-Jack S. Reversible muscle weakness in patients with vitamin D deficiency. *West J Med.* 1997;167(6):435-439.
23. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ.* 2009;339:b3692.
24. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev.* 2012(9):CD007146.
25. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA.* 2010;303(18):1815-1822.
26. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. *JAMA Intern Med.* 2016;176(2):175-183.
27. Campbell MJ, Trump DL. Vitamin D Receptor Signaling and Cancer. *Endocrinol Metab Clin North Am.* 2017;46(4):1009-1038.
28. Koike M, Elstner E, Campbell MJ, et al. 19-nor-hexafluoride analogue of vitamin D3: a novel class of potent inhibitors of proliferation of human breast cell lines. *Cancer Res.* 1997;57(20):4545-4550.
29. Campbell MJ, Gombart AF, Kwok SH, Park S, Koeffler HP. The anti-proliferative effects of 1alpha,25(OH)2D3 on breast and prostate cancer cells are associated with induction of BRCA1 gene expression. *Oncogene.* 2000;19(44):5091-5097.
30. Rejnmark L, Bislev LS, Cashman KD, et al. Non-skeletal health effects of vitamin D supplementation: A systematic review on findings from meta-analyses summarizing trial data. *PLoS One.* 2017;12(7):e0180512.
31. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr.* 2007;85(6):1586-1591.
32. Bolland MJ, Grey A, Gamble GD, Reid IR. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. *Am J Clin Nutr.* 2011;94(4):1144-1149.
33. St John A, Dick I, Hoad K, Retallack R, Welborn T, Prince R. Relationship between calcitrophic hormones and blood pressure in elderly subjects. *Eur J Endocrinol.* 1994;130(5):446-450.
34. Vaidya A, Forman JP. Vitamin D and hypertension: current evidence and future directions. *Hypertension.* 2010;56(5):774-779.
35. Beveridge LA, Struthers AD, Khan F, et al. Effect of Vitamin D Supplementation on Blood Pressure: A Systematic Review and Meta-analysis Incorporating Individual Patient Data. *JAMA Intern Med.* 2015;175(5):745-754.
36. Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. *J Hypertens.* 2009;27(10):1948-1954.
37. Scragg RKR. Overview of results from the Vitamin D Assessment (ViDA) study. *J Endocrinol Invest.* 2019;42(12):1391-1399.
38. Vimaleswaran KS, Cavadino A, Berry DJ, et al. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. *Lancet Diabetes Endocrinol.* 2014;2(9):719-729.
39. Vanherwegen AS, Gysemans C, Mathieu C. Regulation of Immune Function by Vitamin D and Its Use in Diseases of Immunity. *Endocrinol Metab Clin North Am.* 2017;46(4):1061-1094.
40. Stoffels K, Overbergh L, Giulietti A, Verlinden L, Bouillon R, Mathieu C. Immune regulation of 25-hydroxyvitamin-D3-1alpha-hydroxylase in human monocytes. *J Bone Miner Res.* 2006;21(1):37-47.

41. Korf H, Wenes M, Stijlemans B, et al. 1,25-Dihydroxyvitamin D3 curtails the inflammatory and T cell stimulatory capacity of macrophages through an IL-10-dependent mechanism. *Immunobiology.* 2012;217(12):1292-1300.
42. Waisman A, Hauptmann J, Regen T. The role of IL-17 in CNS diseases. *Acta Neuropathol.* 2015;129(5):625-637.
43. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *Lancet Respir Med.* 2017;5(11):881-890.
44. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PLoS One.* 2020;15(9):e0239252.
45. Hoel DG, de Gruijl FR. Sun Exposure Public Health Directives. *Int J Environ Res Public Health.* 2018;15(12).
46. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer.* 2005;41(1):45-60.
47. van der Rhee HJ, de Vries E, Coebergh JW. Regular sun exposure benefits health. *Med Hypotheses.* 2016;97:34-37.
48. Edstrom DW, Linder J, Wennersten G, Brismar K, Ros AM. Phototherapy with ultraviolet radiation: a study of hormone parameters and psychological effects. *J Eur Acad Dermatol Venereol.* 2010;24(4):403-409.
49. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension.* 1997;30(2 Pt 1):150-156.
50. Lindqvist PG, Epstein E, Nielsen K, Landin-Olsson M, Ingvar C, Olsson H. Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort. *J Intern Med.* 2016;280(4):375-387.
51. Holick MF. Vitamin D for health and in chronic kidney disease. *Semin Dial.* 2005;18(4):266-275.
52. Mowbray M, McLintock S, Weerakoon R, et al. Enzyme-independent NO stores in human skin: quantification and influence of UV radiation. *J Invest Dermatol.* 2009;129(4):834-842.
53. Oplander C, Volkmar CM, Paunel-Gorgulu A, et al. Whole body UVA irradiation lowers systemic blood pressure by release of nitric oxide from intracutaneous photolabile nitric oxide derivates. *Circ Res.* 2009;105(10):1031-1040.
54. Kapil V, Gupta AK. Solar UV Radiation: A Potential Modifiable Risk Factor for Hypertension. *J Am Heart Assoc.* 2020;9(5):e015627.
55. Holick MF. Chapter 2 A perspective on the beneficial effects of moderate exposure to sunlight: bone health, cancer prevention, mental health and well being. In: Paolo UG, ed. *Comprehensive Series in Photosciences Sun Protection in Man.* Volume 3 ed.: Elsevier; 2001:11-37.
56. Levins PC, Carr DB, Fisher JE, Momtaz K, Parrish JA. Plasma beta-endorphin and beta-lipoprotein response to ultraviolet radiation. *Lancet.* 1983;2(8342):166.
57. Sansone RA, Sansone LA. Sunshine, serotonin, and skin: a partial explanation for seasonal patterns in psychopathology? *InnovClin Neurosci.* 2013;10(7-8):20-24.
58. Alpert JS. Sunshine: clinical friend or foe? *Am J Med.* 2010;123(4):291-292.
59. Slominski A, Wortsman J. Neuroendocrinology of the skin. *Endocr Rev.* 2000;21(5):457-487.
60. Slominski A, Wortsman J, Tobin DJ. The cutaneous serotoninergic/melatoninergic system: securing a place under the sun. *FASEB J.* 2005;19(2):176-194.
61. Skobowiat C, Postlethwaite AE, Slominski AT. Skin Exposure to Ultraviolet B Rapidly Activates Systemic Neuroendocrine and Immunosuppressive Responses. *Photochem Photobiol.* 2016.

62. Seiffert K, Granstein RD. Neuropeptides and neuroendocrine hormones in ultraviolet radiation-induced immunosuppression. *Methods.* 2002;28(1):97-103.
63. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96(7):1911-1930.
64. Gallagher JC. Vitamin D and aging. *Endocrinol Metab Clin North Am.* 2013;42(2):319-332.
65. Chel VG, Ooms ME, Popp-Snijders C, et al. Ultraviolet irradiation corrects vitamin D deficiency and suppresses secondary hyperparathyroidism in the elderly. *J Bone Miner Res.* 1998;13(8):1238-1242.
66. Chel V, Wijnhoven HA, Smit JH, Ooms M, Lips P. Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents. *Osteoporos Int.* 2008;19(5):663-671.
67. Evaluation of dietary reference values for vitamin D. Health Council of the Netherlands: The Hague. publication no. 2012/15E. In:2012.
68. Ross AC, Manson JE, Abrams SA, et al. The 2011 Dietary Reference Intakes for Calcium and Vitamin D: what dietetics practitioners need to know. *J Am Diet Assoc.* 2011;111(4):524-527.
69. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. In. Washington,D.C.: The National Academies Press; 2010.
70. Brouwer-Brolsma EM, Bischoff-Ferrari HA, Bouillon R, et al. Vitamin D: do we get enough? A discussion between vitamin D experts in order to make a step towards the harmonisation of dietary reference intakes for vitamin D across Europe. *Osteoporos Int.* 2013;24(5):1567-1577.
71. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr.* 2000;72(3):690-693.
72. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Rev Endocr Metab Disord.* 2017;18(2):153-165.