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The story of a vitamin for bone health that upgraded to hormone for systemic good health

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Abstract. The discovery of Vitamin D is a multi-step history started in 1650 and culminated in 1963 with the determination of its chemical structure. The diffusion of rickets in North Europe and North America was the first reason for experimental studies. Nevertheless, in the last decades new potential actions have been revealed. Besides bone and intestine, the Vitamin D receptors have been demonstrated in different organs such as the brain, prostate, breast, colon, immune system cells, smooth muscle and heart. Not totally fulfilling the criteria of a vitamin, Vitamin D is actually considered a pleiotropic hormone with endocrine and paracrine actions. The current evidences support the role of Vitamin D in skeletal health and suggest that the treatment of Vitamin D deficiency should be desirable to reduce the risk of chronic health diseases.

Key words: Vitamin D, Vitamin D deficiency, bones, metabolic disease, health benefits

Vitamin D: general features

Vitamin D is likely to be one of the oldest existing hormones on the Hearth (1). Indeed, Vitamin D photosynthesis has been demonstrated in fossils existing 750 millions years ago (1, 2). In normal physiological condition the activation of Vitamin D is a multistep pathway. All mammals can generate adequate Vitamin D levels through the sunlight activation of 7-dehydrocholesterol in the skin, followed by two hydroxylations in liver ($1,25(OH)_2$Vitamin D or cholecalciferol) and kidney (calcitriol). Events modifying Ultraviolet B (UVB) wave exposure (e.g. skin hyperpigmentation, sunscreen, zenith angle of the sun) may impair the photosynthesis of pre-Vitamin D (1). As a consequence, Vitamin D deficiency is "epidemic" in most adults, who are not exposed to adequate amount of sunlight (3, 4).

The discovery of the fourth Vitamin: the "Antirachitic Factor"

The word "rickets" first appeared in 1634 when the disease figured in the "Annual Bill of Mortality" of London City (5). In a book published in 1650, Francis Glisson provided the most detailed description of the disease, responsible of bone deformation and fractures in infants and children (5). The raising number of cases in North Europe and America during the Industrial Revolution supported intensive speculations on its pathogenesis and treatment (2).

It was just in 1918-19 that Mellanby conducted conclusive experiments on the role of diet in the etiology and treatment of rickets (6, 7) (Figure 1). He tested 4 diets in a group of puppies, discovering that just rich in fat-soluble Vitamin A food (cod-liver oil, butter, and whole milk) could prevent rickets (6). In

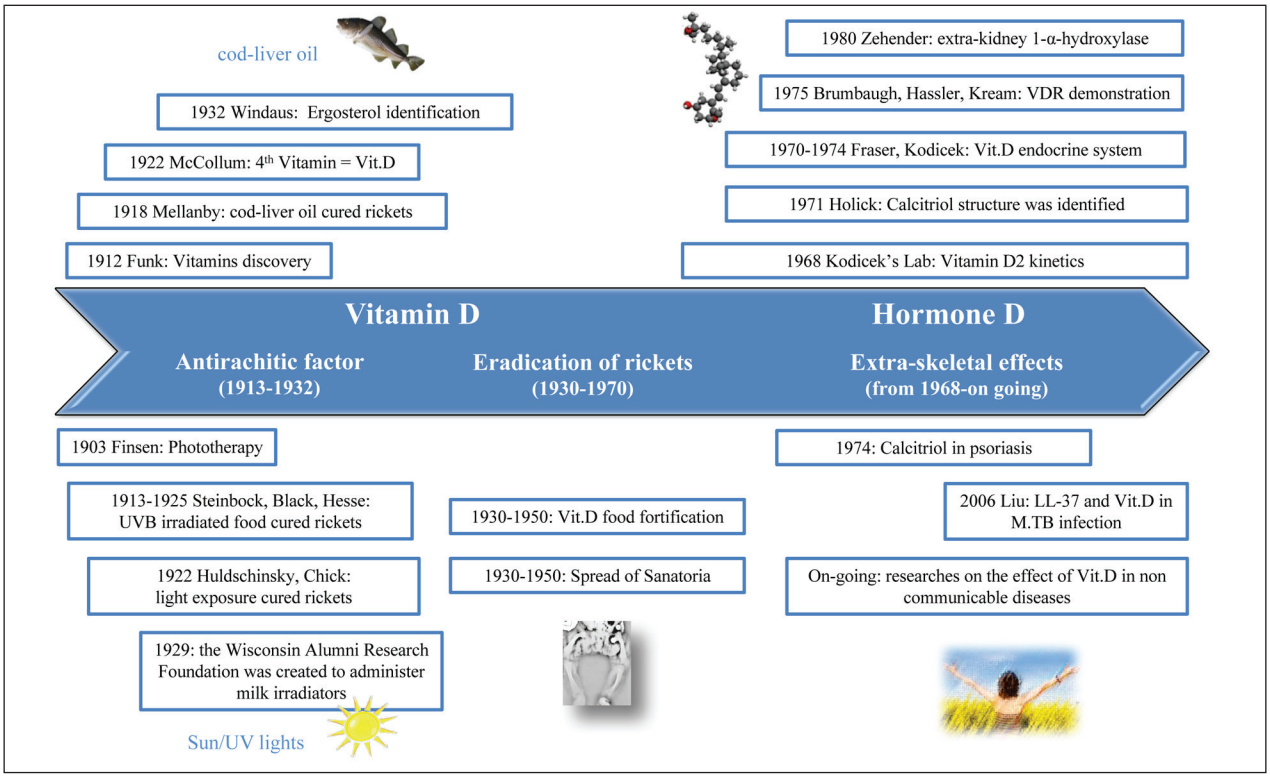

Figure 1. Hystorical discoveries about Vitamin D, related both to its role in treating rickets and in general health. The diagram is divided in three parts: 1) discovery of a way to prevent and cure rickets, 2) eradication of rickets through food fortification and sun exposure, 3) paracrine/autocrine effects of Vitamin D. M.TB = *Mycobacterium tuberculosis*.

1922 McCollum discerned the real "antirachitic factor", proving that the inclusion of cod-liver oil in diet could favor bone growth even after denaturalization of Vitamin A (8). McCollum concluded the "antirachitic substance" was distinct from fat-soluble Vitamin A and that its "specific property was to regulate the metabolism of the bones" (8). In the meanwhile, awareness rose on the health benefits of light exposure. It was largely observed that children grew up along the European coasts had healthier skeletal structure than children in towns (2, 3).

Chick and Huldshinsky in 1919 independently demonstrated that rickets could be prevented by lights exposure. This intuition supported the application of Finsen chemical light lamp to treat rickets (2). Accordingly, Steinbock and Blant in 1925 cured rickets irradiating food and recommended food irradiation to enhance the "antirachitic effect" (9). It happens a few years later, in 1928, that the Nobel Prize Windaus identified a plant steroid from ergot able to cure rickets when irradiated (2) (Figure 1). According to Windaus the steroid isolated from plants was similar to ergosterol isolated in animals (2). The 7-dehydrocholesterol later isolated from the skin, could be transformed in a vitamin by irradiation (10). Since the purified ergosterol was the fourth vitamin discovered, it was called "Vitamin D" (11, 12, 13). The chemical identification of Vitamin D precursor in the skin confirmed the hypothesis of epidermal synthesis (14). Despite these discoveries, rickets cases were increasing. As a result of the long time spent in factories, workers' exposure to sunlight remained poor. Nevertheless, the use of cod-liver oil was still inadequate (2). From 1930 Phototherapy Spas (Sanatoria) become very popular in Europe and North America (2). Concomitantly, US Government imposed the fortification of food with Vitamin D (initially bread and milk and later also beer) managing to eradicate rickets (2). In the 50s, food fortification was forbidden because of the uncontrolled amount of Vitamin D in milk (2, 5).

Vitamin D and bone metabolism

In 1920 Nicolaysen observed a better absorption of calcium in animals on low-calcium-diet and postulated the existence of an "endogenous factor" able to regulate intestinal calcium absorption (2). Administering known doses of radiolabeled Vitamin D_2, Kodicek provided a better description of the process (15). In 1971, De Luca identified the first active metabolite ($1,25(OH)_2$Vitamin D_3 or calcitriol) (Figure 2). Interestingly, he found that anephritic animals were unable to produce active Vitamin D metabolites. Some years later, Holick definitely demonstrated that the final activation of Vitamin D took place in the proximal convolute tubule (2). The metabolizing enzyme was discovered to be a 1-α-hydroxylase (CYP27B1) by three different groups (3, 15-19).

Between 1969-1984 it was discovered that most of Vitamin D actions were mediated by the nuclear Vitamin D Receptor (VDR), whose crystal structure has been recently identified, acting as a ligand-activated transcription factor (2, 20-24).

Boyle and De Luca demonstrated that a low calcium-diet enhances the synthesis of Vitamin D_3, raising serum levels (16). When VDRs were discovered in parathyroid gland, it became clear that Vitamin D_3 could suppress the secretion of Parathyroid hormone (PTH) (16, 25). Vitamin D analogs were formulated for commercialization (16).

Garabedian showed the existence of a feedback mechanism involving serum calcium, Vitamin D and PTH. This system corresponded to Nicolaysen's endogenous factor (2, 16). Decrease in serum calcium rapidly induced the activation of Vitamin D through PTH secretion, whereas high calcium levels suppressed the conversion of pre-Vitamin D (1, 2). Calcitriol in turn promoted intestinal and renal calcium absorption, enhancing bone resorption and calcium

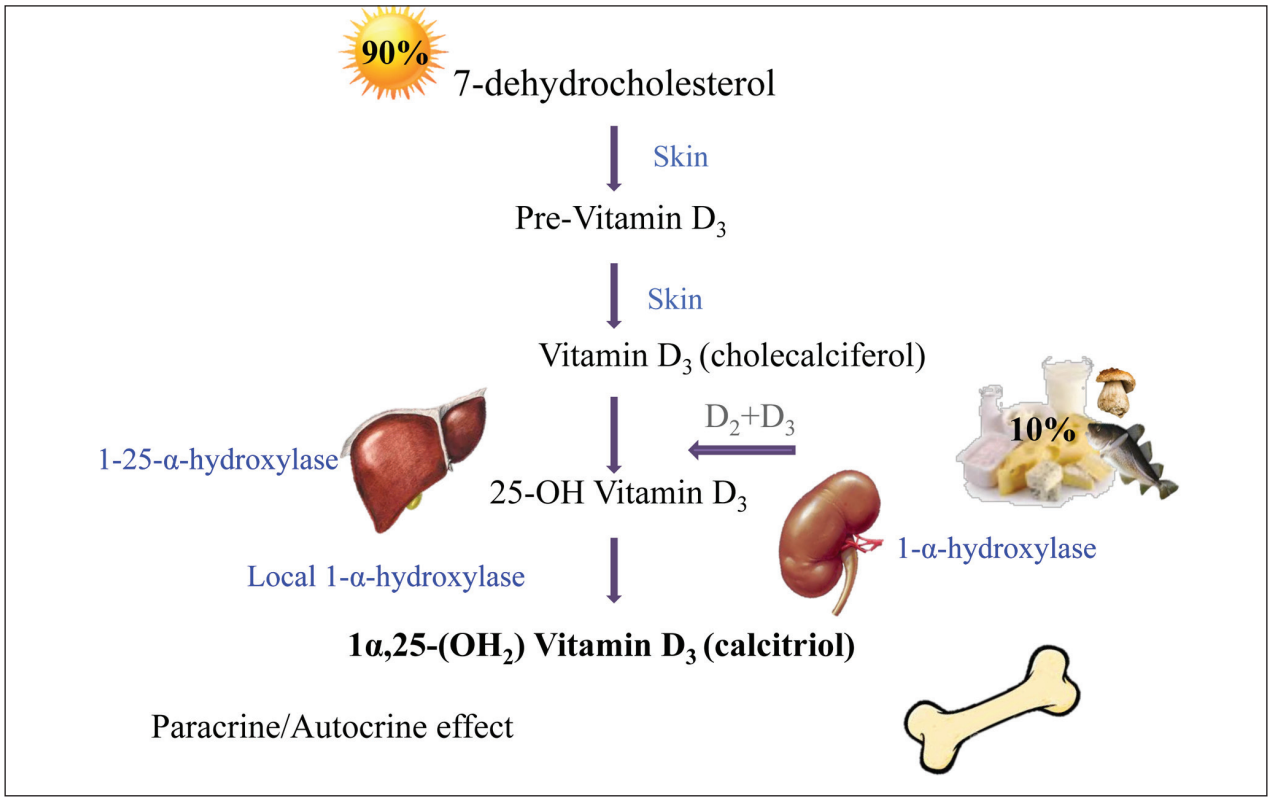

Figure 2. Systemic active Vitamin D (calcitriol) derives from a multistep process of activation (sunlight activation of 7-dehydrocholesterol in the skin, followed by two hydroxylations in liver and kidney). Vitamin D may also be activated locally for paracrine/autocrine function, regulating general health.

freeing (14). Calcitriol together with PTH regulates phosphate levels (Pi) by modulating intestinal and renal Pi reabsorption and bone metabolism (17). As initially demonstrated by Heyman in 1928 (18), up to 30% of Pi is absorbed in intestine (17). According to De Luca experiments on nepherectomized animals the process was mediated by the active metabolite (19).

Extra-skeletal functions

The observation of higher sensitivity to Vitamin D in patients suffering from chronic granulomatous diseases such as sarcoidosis and tuberculosis paved the way for the first experiments on extra-skeletal roles of Vitamin D. In 1982 it was observed that macrophages in the granolumatous tissues convert pre-Vitamin D in calcitriol (3). With the advent of Molecular Biology, transcripts of CYP27B1 and VDR were found in tissues not previously recognized as sites of Vitamin D synthesis (23, 26).

Additionally, it was discovered that VDR was involved in the selective modulation of tissue-specific gene transcription through heterodimerization with retinoid X receptor, recruitment of nuclear proteins and binding to vitamin D response elements (27). It became progressively clear that genetic alterations of VDR affected calcium metabolism, cell proliferation and the immune system (27). By the end of the 90th century, polymorphisms of VDR gene were localized between the 8 and 9 exons by restriction enzymes, and later, applying the sequences approach, new polymorphisms were discovered (27, 28). Actually, polymorphisms in the VDR gene occur frequently, but the significance is not completely understood and it is still object of intensive research.

Osteomalacic myopathy

The initial descriptions of rickets mentioned muscular weakness, especially in children (29, 30). Proximal myopathy with severe muscular impairment has been observed in subjects with severe Vitamin D deficiency (29). The term "osteomalacic myopathy" was definitely coined in 1965 to describe proximal muscular weakness (30).

Lesser severe muscle changes have been observed in mild deficiency (29). Recently, the effect of vitamin D supplementation in deficient athletes or not-athletes returned ambiguous results, being conditioned by basal Vitamin D levels (29, 31). Three recent meta-analysis observed that the beneficial effects of Vitamin D supplementation were higher in elderly subjects, with improvement of balance and muscle function (29, 31, 32). Actually, Vitamin D deficiency is prevalent in institutionalized older subjects and may contribute to the development of age-related sarcopenia and to increase risk of fall. Bischoff-Ferrari demonstrated an impairment of Vitamin D photosynthesis and renal activation with aging (33). Therefore, older people could be more exposed to Vitamin D deficiency and could benefit the most from adequate supplementation (29).

The "bidirectional" relationship between Vitamin D and the skin

The earliest records about the relationship between skin diseases and sun exposure date back to the ancient Egyptians and Indians (34). Surprisingly, more than 3500 years ago, Egyptians treated Vitiligo by associating sunlight exposure and the ingestion of boiled weed (35). In the second Century BC, travelling to Egypt, Hippocrates discovered the beneficial effect of sun. Back to Greece, he recommended the exposure to sunlight for health benefit (34). In 1877, Downs and Blunt demonstrated that light exposure could prevent fungal growth *in vitro*.

In 1985, MacLaughlin reported that psoriatic fibroblasts were partially resistant to the anti-proliferative effects of calcitriol. This finding encouraged to speculate that calcitriol could be effective in the treatment of psoriasis (35). Concomitantly, Morimoto and Kumahara incidentally observed the remission of psoriatic lesions in a patient treated with oral Vitamin D for osteoporosis. Thereafter, they demonstrated that oral treatment with calcitriol could significantly improve psoriasis (35) (Figure 1).

In the last years, numerous studies reported that topical Vitamin D analogs (e.g. calcitriol, calcipotriol, tacalcitol, hexafluoro-1,25-dihydroxyvitamin D_3) are effective and safe in the treatment of psoriasis (35). In

1998 Parsad published effectively combined PUVAsol and topical calcipotriol; these findings were confirmed by later studies (36, 38).

Cardiovascular health

The history of the relationship between vitamin D and cardiovascular health is quite recent. In 1981, Robert Scragg (39) first hypothesized that the decrease of cardiovascular disease mortality and morbidity in summer season might be a consequence of cardiovascular-protective effects of vitamin D through a direct action on the platelet, or mediated by a change in calcium metabolism. Over the last three decades the possible role of vitamin D in cardiovascular diseases has become a particularly intriguing topic (40).

Both the enzyme 1-alpha-hydroxylase, and VDR are found in the vessels and in the heart, namely in cardiomyocytes, cardiac fibroblasts, vascular smooth muscle cells, and vascular endothelial cells. This knowledge is derived from experimental models published from the second half of the 80s. Walters and coworkers, in 1986 demonstrated the presence of specific receptors for 1,25-dihydroxyvitamin D3 in low salt chromatin preparations from normal rat hearts (41). Some years later, Bidmon and coworkers (42) reported that receptors for vitamin D exist in the heart of mice, predominantly in the right atrium. In 2002, Li and coworkers observed that a mouse with a complete deletion of the VDR gene demonstrates both hypertension and cardiac hypertrophy (43). In subsequent years, in particular between 2005 and 2008, a further step forward is derived from studies in knock-out mice for VDR or 1-αhydroxylase, which suffer from cardiovascular pathologies including arterial hypertension, myocardial hypertrophy and increased thrombogenicity (44, 45, 46). In rat models, it was shown that early life vitamin D deficiency is associated with impaired vascular endothelial and smooth muscle cell function (47). In parallel with experimental animal studies, in 1996 O'Connell and Simpsom (48) identified the receptor protein for $1,25(OH)_2D_3$ in tissue from two human hearts by using an antibody directed against the recombinant Vitamin D3 receptor, suggesting a role of Vitamin D in cardiovascular pathophysiology. A few years later, Somjen and coworkers (44) identified the expression of 25-hydroxyvitamin D_3 – 1-alpha-hydroxylase in human vascular smooth muscle cells and in 2008, Chen and coworkers, reported an increased expression of the Vitamin D receptor in the human hypertrophic heart (45). In addition to the preclinical observations, there are numerous clinical evidences linking Vitamin D to cardiometabolic risk factors and cardiovascular diseases. Since the 1970s, an increasing interest in the relationship between vitamin D and coronary heart disease has emerged. Among the first studies there is a Danish study published in 1978 (46), which found that low Vitamin D levels were significantly associated with angina and myocardial infarction. Low Vitamin D levels were associated with a higher risk of myocardial infarction in the Health Professionals Follow-up Study (47), including 18,225 US men between 1993 and 1999. Data collected from studies performed in the US and Europe between 1970 and 2003 were analyzed in a meta-analysis published in 2012, evaluating the risk of ischemic heart disease and early death. The Authors observed an increasing risk of ischemic heart disease, myocardial infarction, and early death with decreasing plasma 25-hydroxyvitamin D levels (48). In the same years, particularly between 2007 and 2011, interesting epidemiological data were proposed in the literature about the relationship between vitamin D status and blood pressure, based on the NHANES III 1988-1994 (49) and NHANES 2003-2006 (50), showing an inverse association. Furthermore, an inverse association between vitamin D status and risk of incident hypertension was observed in men from the Health Professionals Follow-up Study and in women from the Nurses' Health Study, suggesting a pooled relative risk of 3.18 (51). Furthermore, in hypertensive patients several studies demonstrated a link between low 25 (OH) Vitamin D concentrations and cardiovascular events (52).

When we consider the spectrum of cardiovascular diseases and their risk factors, an analysis of NHANES III 1988-1994 (53) showed that low Vitamin D was associated with cardiovascular diseases and with some risk factors, such as diabetes mellitus, obesity, and hypertriglyceridemia (54). The analysis of data from NHANES 2001-2004 showed a high prevalence of hypovitaminosis D in patients with coronary heart disease and heart failure (55). In 2012 Wang and

coworkers published a meta-analysis of 19 prospective studies in 65,994 individuals, demonstrating a generally linear and inverse association between circulating 25(OH) Vitamin D levels in the range of 20-60 nmol/l and risk of cardiovascular diseases (56).

To date, experimental and clinical data suggest that Vitamin D system may play an important role in the maintenance of cardiovascular health (57), but the causality of the relationship between Vitamin D deficiency and cardiovascular diseases remains to be established. Some, but not all, observational studies in humans provide support for these experimental findings, raising the possibility that Vitamin D or its analogs might prove useful therapeutically in the prevention or treatment of cardiovascular diseases. Larger randomized clinical trials are needed to support the benefits of Vitamin D therapy in managing patients with cardiovascular disease in the clinic. It is desirable that knowledge in this issue will progress in the near future, when the results of two large ongoing studies will be available, the VITAL trial (VITamin D and OmegA-3 Trial) (58) and the Vitamin D3-Omega3-Home Exercise-Healthy Ageing and Longevity Trial (59).

Vitamin D and the its relationship with cancer

The first reports indicating a role of Vitamin D in anticancer activity dated on 1981, when Colston et al. demonstrated that the Vitamin D_3 was able to inhibit the growth of melanoma tumor cells in vitro (60). Later in that year Abe and his group indicated that calcitriol can induce the differentiation of mouse HL60 leukaemia cells towards the macrophage cell type (61). Then, the antineoplastic effects of Vitamin D_3 have been reported both *in vitro* and *in vivo*, in various malignancies, in particular in breast, prostate and colorectal cancer (62). The first epidemiological report that linked a lack of sunlight exposure to colon cancer risk was in 1980 from Garland et al. for colon cancer (63). Afterwards, other epidemiological studies suggest an inverse correlation between blood Vitamin D_3 levels and increased incidence of several types of cancers, but associations have most consistently been observed for colorectal cancer (64). Since then, several distinct mechanism underlying the anticancer effects of calcitriol have been elucidated by experimental data, such as: anti-proliferative effects, induction of apoptosis, stimulation of differentiation, anti-inflammatory effects, inhibition of invasion and metastasis and inhibition of angiogenesis in different types of cancers (65). More recently, emerging data from preclinical and some clinical studies seem to suggest that avoiding deficiency and adding vitamin D_3 supplements or analogs might be a way to reduce cancer incidence and improve cancer prognosis and outcome (65). This consideration may also have clinical relevance on anticancer therapies using monoclonal antibodies approach, possibly due to the effects of the Vitamin D_3 on the immune system, through the antibody-dependent cell-mediated cytotoxicity mechanism either on natural killer cells (66, 67) or on macrophages (68).

However, several immune cell types of both innate and adaptive cells, including T cells, express VDR and the key enzyme CYP27B1, that render immune cells able to produce on its own the active form of vitamin, i.e. $1,25(OH)_2D$. Furthermore, a growing body of evidence suggests an important immune-modulating role of vitamin D in the T-cell differentiation and their effector functions (69). These mechanisms seem to recapitulate the role of vitamin D3-VDR interaction in the setting of proper immune cell functions and impeding autoimmune disorder development (70). Finally, recent data seem to postulate a possible role for vitamin D blood serum levels as a predictive element in the immune-checkpoint blockade using anti-CTLA-4, anti-PD-1 and anti-PD-L1 monoclonal antibodies in melanoma metastatic patients, highlighting a potential positive antigen-dependent role of vitamin D in cancer treatments (71).

Conclusion

Progressively it has been acquired that Vitamin D is important for general health (16). Interestingly, besides being essential in skeletal health, Vitamin D plays a role in cellular proliferation, growth and differentiation. Endocrine, paracrine and autocrine functions have been discovered. The history of Vitamin D research, after more than 400 years of research, is definitely not completed.

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References

1. Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and skin physiology: a D-lightful story. J Bone Miner Res 2007; 22(suppl. 2): V28-V33.
2. DeLuca HF. (Ed.) Vitamin D. In: Feldman D, Pike J W, Bouillon R, Giovannucci E, Goltzman D, Hewison M. Academic Press 2017; 4th Edition (1).
3. Holick MF. Evolution and function of vitamin D. Recent Results Cancer Res 2003; 164: 3-28.
4. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357(3): 266-81.
5. O'Riordan JL, Bijvoet OL. Rickets before the discovery of vitamin D. Bonekey Rep 2014; 3:478.
6. Rajakumar K. Vitamin D, cod-liver oil, sunlight and rickets: a historical perspective. Paediatrics 2003; 112(2): e132-5.
7. Mellanby E. The part played by an accessory factor in the production of experimental rickets. J Physiology 1918; 50: 1915-6.
8. McCollum EV, Simmonds N, Becker JE, Shipley PG. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. J Biochem Chem 1922; 53: 293-8.
9. Steenbock H, Black A. Fat soluble vitamins XVII. The induction of bone promoting and calcifying properties in a ration by exposure to ultraviolet light. J Biochem Chem 1924; 61: 405-22.
10. Wolf G. The discovery of vitamin D: the contribution of Adolf Windaus. J Nutr 2004; 134(6): 1299-302.
11. Funk C. The etiology of deficiency diseases. J State Med 1912; 20: 341-54.
12. Semba RD. The discovery of the Vitamins. Int J Vitam Nutr Res 2012; 82(5): 310-5.
13. Bill C, Massengale ON, Hickman KCD, Gray EL. A new vitamin D in cod liver oil. J Biochem Chem 1938; 126: 241-4.
14. Holick MF, MacLaughlin JA, Clark MB, Holick SA, Potts JT Jr, Anderson RR, Blank IH, Parrish JA, Elias P. Photosynthesis of previtamin D3 in human skin and the physiologic consequences. Science 1980; 210: 203-5.
15. Fraser D, KodiceK De. Unique biosynthesis by kidney of a biological active vitamin D metabolite. Nature 1970; 228: 764-6.
16. DeLuca HF. History of the discovery of vitamin D and its active metabolites. Bionekey Rep 2014; 3: 479.
17. Jacquillet G, Unwin RJ. Physiological regulation of phosphate by vitamin D, parathyroid hormone (PTH) and phosphate (Pi). Pflugers Arch 2018; Nov 5. doi: 10.1007/s00424-018-2231-z.
18. Nikolaysen R, Eeg-Larsen N. Vitamin D and Homones. The Biochemestry and physiology of vitamin D. Academic Press Inc. Publishers New York 1953; 11: 38-42.
19. Rizzoli R, Fleisch H, Bonjour JP. Role of 1,25-dihydroxyvitamin D_3 on intestinal phosphate absorption in rats with a normal vitamin D supply. J Clin Invest 1977; 639-47.
20. Brumbaugh PF, Haussler MR. Specific binding of 1alpha,25-dihydroxycholecalciferol to nuclear components of chick intestine. J Biol Chem 1975; 250: 1588-94.
21. Lawson DE, Wilson PW. Intranuclear localization and receptor proteins for 1,25-dihydroxycholecalciferol in chick intestine. Biochem J 1974; 144: 573-83.
22. Haussler MR, Myrte JF, Norman AW. The association of a metabolite of vitamin D3 with intestinal mucosa chromatin, in vivo. J Biol Chem 1968; 243: 4055-64.
23. Norman AW, Roth J, Orci L. The vitamin D endocrine system: steroid metabolism, hormone receptors and biological response (calcium binding proteins). Endocr Rev 1982; 3: 331-66.
24. Rochel N, Wurts JM, Mitschler A, Klaholz B, Moras D. The crystal structure of the nuclear receptor for vitamin D bound to its natural ligand. Mol Cell 2000; 5(1): 173-9.
25. Demay MB, Kiernan MS, DeLuca HF, Kronenberg HM. Sequences in the human parathyroid gene that bind the 1,25-dihydroxyvitamin D3 receptor and mediate transcriptional repression in response to 1,25-dihydroxyvitamin D3. Proc Nat Acad Sci USA 1992; 89(17): 8097-101.
26. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, Hewison M. Extrarenal expression of 25-Hydroxyvitamin D(3)-1 alpha-hydroxylase. J Clin Endocrinol Metab 2001; 86(2): 888-94.
27. Norman AW. Minireview: vitamin D receptor: new assignments for an already busy receptor. Endocrinology 2006; 147(12): 5542-8.
28. Gross C, Eccleshall TR, Malloy PI, Villa ML, Marcus R, Feldman D. The presence of a polymorphism at the translational initiation site of the vitamin D gene is associated with low bone mineral density in postmenopausal Mexican-American women. J Bone Miner Res 1996; 11(12): 1850-5.
29. Gunton J, Girgis CM. Vitamin D and muscle. Bone Rep 2018; 8: 163-7.
30. Dastur DK, Bomi MG, Waia NHDesai MM, Bharucha EP. Nature of muscular change in osteomalacia: light- and electron-microscope observations. Plates CV-CCII 1975; 117: 221-8.
31. Stockon KA, Mengersen K, Parats JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and met-analysis. Osteopors Int 2011; 22: 859-71.
32. Muir SW, Montero Odasso. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 2011; 59: 2291-300.
33. Bischoff-Ferrari HA, Borchers M, Gudat F, Dürmüller U, Stähelin HB, Dick W. Vitamin D receptor expression in human muscle tissue descrease with age. J Bone Min Res 2004; 19: 265-9.

34. Jarret P, Scragg R. A short history of phototherapy, vitamin D and skin disease. Photochem Photobiol Sci 2017; 16(3): 283-90.
35. Honigsmann H. History of Phototherapy in dermatology. Photochem Photobiol Sci 2013; 12(1): 16-21.
36. Mostafa WZ, Hegazy RA. Vitamin D and the skin: Focus on a complex relationship: A review. J Adv Res 2015; 6(6): 793-804.
37. Kovacs R. Electrotherapy and the Elements of Light Therapy. Philadephia: Lea & Febiger, 1932.
38. Parsad D, Saini R, Verma N. Combination of PUVAsol and topical calcipotriol in vitiligo. Dermatology 1998; 197(2): 167-70.
39. Scragg R. Seasonality of cardiovascular disease mortality and the possible protective effect of ultra-violet radiation. Inter J Epidemiol 1981; 10(4): 337-41.
40. Pilz S, Tomaschitz A, März W, et al. Vitamin D, cardiovascular disease and mortality. Clin Endocrinol 2011; 75: 575-84.
41. Walters MR, Wicker DC, Riggle PC. 1,25-Diydroxyvitamn D3 receptors identified in the rat heart. J Mol Cell Cardiol 1986; 18(1): 67-72.
42. Bidmon HJ, Gutkowska J, Murakami R, Stumpf WE. Vitamin D receptor in heart: effects on atrial natriuretic factor. Experimentia 1991; 47(9): 958-62.
43. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002; 110(2): 229-38.
44. Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, Jaccard N, Knoll E, Stern N. 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation 2005; 111: 1666-71.
45. Chen S, Glenn DJ, Ni W, Grigsby CL, Olsen K, Nishimoto M, Law CS, Gardner DG. Expression of the vitamin D receptor is increased in the hypertrophic heart. Hypertension 2008; 52: 1106-12.
46. Lund B, Badskjaer J, Lund B, Soerensen O. Vitamin D and ischaemic heart disease. Horm Metab Res 1978; 10(6): 553-6.
47. Giovannucci E, Liu Y, Hollis B, Rimm E. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Inter Med 2008; 168: 1174-80.
48. Brondum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG. 25-hydroxyvitamin D levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. Arterioscler Thromb Vasc Biol 2012; 32: 2794-802.
49. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. Am J Hypertens 2007; 20: 713-9.
50. Zhao G, Ford ES, Li C, Kris-Etherton PM, Etherton TD, Balluz LS. Independent associations of serum concentrations of 25-hydroxyvitamin D and parathyroid hormone with blood pressure among US adults. J Hypertens 2010; 28: 1821-8.
51. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension 2007; 49: 1063-9.
52. Wang TJ, Pencina MJ, Booth SL, Jaques PF. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008; 117: 503-11.
53. Kendrick J. Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutritional Examination Survey. Atherosclerosis 2009; 205: 255-60.
54. Martini LA, Wood RJ. Vitamin status and the metabolic syndrome. Nutr Rev 2006; 64: 479-86.
55. Kim D, Sabour S, Sagar U, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). Am J Cardiol 2008; 102: 1540-4.
56. Wang L, Song Y, Manson JAE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating of 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 2012; 5(6): 819-29.
57. Piantanida E, Gallo D, Veronesi G, Dozio E, Trotti E, Lai A, Ippolito S, Sabatino J, Tanda ML, Toniolo A, Ferrario M, Bartalena L. Cardiometabolic healthy and unhealthy obesity: does vitamin D play a role? Endocr Connect 2017; 6: 943-51.
58. Manson JE, Bassuk SS, Lee IM, Cook NR, Christen WG, Bubes VY, Gordon DS, Copeland T, Friedenberg G, D'Agostino DM, Ridge CY, MacFadyen JG, Kalan K, Buring JE. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. Contemp Clin Trials 2012; 33(1): 159-71.
59. CORDIS. DO-Health Report Summary, Universitaet Zuerich, Switzerland, 2017.
60. Colston K, Colston MJ, Feldman D. 1,25-dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture. Endocrinology 1981; 108: 1083–6.
61. Abe E, Miyaura C, Sakagami H, Takeda M, Konno K, Yamazaki T, Yoshiki S, Suda T. Differentiation of mouse myeloid leukemia cells induced by 1 alpha,25-dihydroxyvitamin D3. Proc Nat Acad Sci USA 1981; 78: 4990–4.
62. Leyssens C, Verlinden L, Verstuyf A. Antineoplastic effects of 1,25(OH)2D3 and its analogs in breast, prostate and colorectal cancer. Endocr Relat Cancer 2013; 20: R31–R47.
63. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? Intern J Epidemiol 1980; 9: 227–31.

64. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2011; 155: 827–38.
65. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ, The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer 2014; 14(5): 342-57.
66. Bittenbring JT, Neumann F, Altmann B, Takeda M, Konno K, Yamazaki T, Yoshiki S, Suda T. Vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. J Clin Oncol 2014; 3(29): 3242–8.
67. Mortara L, Gariboldi MB, Bosi A, Bregni M, Pinotti G, Guasti L, Squizzato A, Noonan DM, Monti E, Campiotti L. Vitamin D Deficiency has a Negative Impact on Cetuximab-Mediated Cellular Cytotoxicity against Human Colon Carcinoma Cells. Target Oncol 2018; 13(5): 657-65.
68. Bruns H, Büttner M, Fabri M, Mougiakakos D, Bittenbring JT, Hoffmann MH, Beier F, Pasemann S, Jitschin R, Hofmann AD, Neumann F, Daniel C, Maurberger A, Kempkes B, Amann K, Mackensen A, Gerbitz A. Vitamin D-dependent induction of cathelicidin in human macrophages results in cytotoxicity against high-grade B cell lymphoma. Sci Transl Med 2015; 7(282): 282ra47.
69. Kongsbak M, Levring TB, Geisler C, von Essen MR. The vitamin D receptor and T cell function. Front Immunol 2013; 4: 148.
70. Mangin M, Sinha R, Fincher K. Inflammation and vitamin D: the infection connection. Inflamm Res 2014; 63(10): 803–19.
71. Timerman D, McEnery-Stonelake M, Joyce CJ, Nambudiri VE, Hodi FS, Claus EB, Ibrahim N, Lin JY. Vitamin D deficiency is associated with a worse prognosis in metastatic melanoma. Oncotarget 2016; 8(4): 6873–82.

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