
BASIC MEDICAL SCIENCE ARTICLE

Vitamin D and health – a historical overview

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Abstract

Awareness of the importance of skin exposure to UV rays for normal bone growth and systemic health increased with landmark scientific discoveries over the past century. Several Nobel-prize laureates unravelled the steps involved in the activation of 7-dehydrocholesterol to 1,25 (OH)₂ vitamin D (or vit D₃) which is rapidly becoming the most important medical discovery in the past decade. Recent developments in our understanding of the impact of vit D on the immune system, carbohydrate metabolism, and cardiovascular and neoplastic diseases are briefly highlighted.

Key words: vitamin D, cholecalciferol, ergocalciferol, phototherapy, UV light

Historical perspective

Before 1890 it was noticed that children who grew up along the coast in Europe (where sunshine and fresh air are more prevalent) manifested with less stunted skeletal growth and bowing of weight-bearing bones than those dwelling in cities. Niels Ryberg Finsen, a native of the Faroe Islands (south of Iceland) and a medical graduate of the University of Copenhagen in 1890, suffered from Pick's disease which is characterised by progressive thickening of the membranes of the heart, spleen and liver. He lived in a house facing north and believed that his progressive tiredness and ascites were the result of a lack of sunlight. From his early appointment as a tutor in anatomy he collected data on animals seeking sunlight, with a firm conviction of the as yet undiscovered benefits thereof. In simple experiments Finsen demonstrated that rays from the sun and an electrical arc may have strong antimicrobial effects and stimulate tissue health. He proved convincingly the benefit thereof for patients suffering lupus vulgaris (skin tuberculosis) and smallpox (which spread in epidemic proportions through Europe at the time). Finsen soon became known as the

father of phototherapy for which he received the Nobel Prize in 1903.¹ His name was immortalised with other Nobel Prize laureates like Emil von Behring 1901 (serum therapy), Ronald Ross 1902 (malaria infection), Ivan Pavlov 1904 (physiology of digestion) and Robert Koch 1905 (tuberculosis research) who laid significant foundations for modern medicine during the first decade of the twentieth century. Phototherapy clinics where chronic infectious diseases (mainly tuberculosis) and rickets were treated arose in sunny locations such as high in the Alps and high altitude states like Michigan. One such example is the Battle Creek Sanatorium, a health resort for permanently disabled soldiers of the American wars, which was rebuilt by John Harvey Kellogg in 1902 after a devastating fire.

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A change of two letters transformed 'sanatorium' to 'sanitarium' and a new word emphasising wellness was added to the English language. The phototherapy and thermotherapy department, accommodating the first electric light bath, treated notable patients like CW Post (founder of Post Cereals), Amelia Earhart (first female aviator across the Atlantic ocean), Johnny Weissmuller (famous for acting Tarzan), Henry Ford and Mary Lincoln, wife of President Lincoln.² It was soon discovered that sun exposure was as effective as cod liver oil in the treatment of rickets and that glass filtered out the 'health' benefits thereof. (Today we know that glass neutralises the β -fraction of ultraviolet (UV) light required for activation of the precursors of vitamin D.)

The build-up to the discovery of vitamin D (vit D) had a long history and involved many research teams, all of which cannot be acknowledged due to a lack of space. A key experiment was performed in 1922 by McCullum *et al*³ who showed that heated cod liver oil lost its anti-xerophthalmic effect which was known to be the result of a factor A (later named vitamin A) but retained its capacity to cure rickets in rats. Because the water soluble factors discovered at the time were termed vitamin B and the anti-scurvy factor vitamin C, they named the newly discovered factor vit D. A Nobel Prize laureate in 1928 and physician trained in Berlin, Adolf Windaus, who dedicated his scientific career to sterol biochemistry, discovered a plant sterol from ergot (mushrooms) which, when irradiated, cured rickets in rats.⁴

The irradiated product of ergosterol was purified by Windaus and other research teams⁵ and was named vitamin D₂ which in sub-microgram concentrations demonstrated potent anti-rachitic properties. One question however remained. Ergosterol does not occur in humans. How do humans obtain the active form of vit D through exposure to sunlight? In 1937 after exhaustive work and long after his Nobel award, Windaus and Bock⁶ identified 7-dehydrocholesterol in skin of several species. This substance, which was also present in whole milk and liver, was converted to an anti-rachitic agent through irradiation. The irradiated product was named vit D₃ or cholecalciferol. The complete photochemical reaction of ergosterol and cholecalciferol was deciphered in 1955 by Vellus *et al*.⁷

Metabolic activation

A detailed account of the biochemical processes involved in the activation of vit D does not fall within the scope of this article. It is however clear from the diagram presented in *Figure 1* that the activation follows a multi-step pathway involving UV irradiation of the skin and two phases of hydroxylation to 25(OH) vit D (vit D₂) and 1,25(OH)₂ vit D (vit D₃) in the liver and kidney respectively. The metabolically active form is vit D₃. Vit D is a fat-soluble substance with a half-life of approximately three weeks in the 25(OH) vit D stage and only several hours as 1,25(OH)₂ vit D. Its fat solubility results in higher dosages required to achieve normal blood levels in obese persons compared to those with a normal body fat composition.

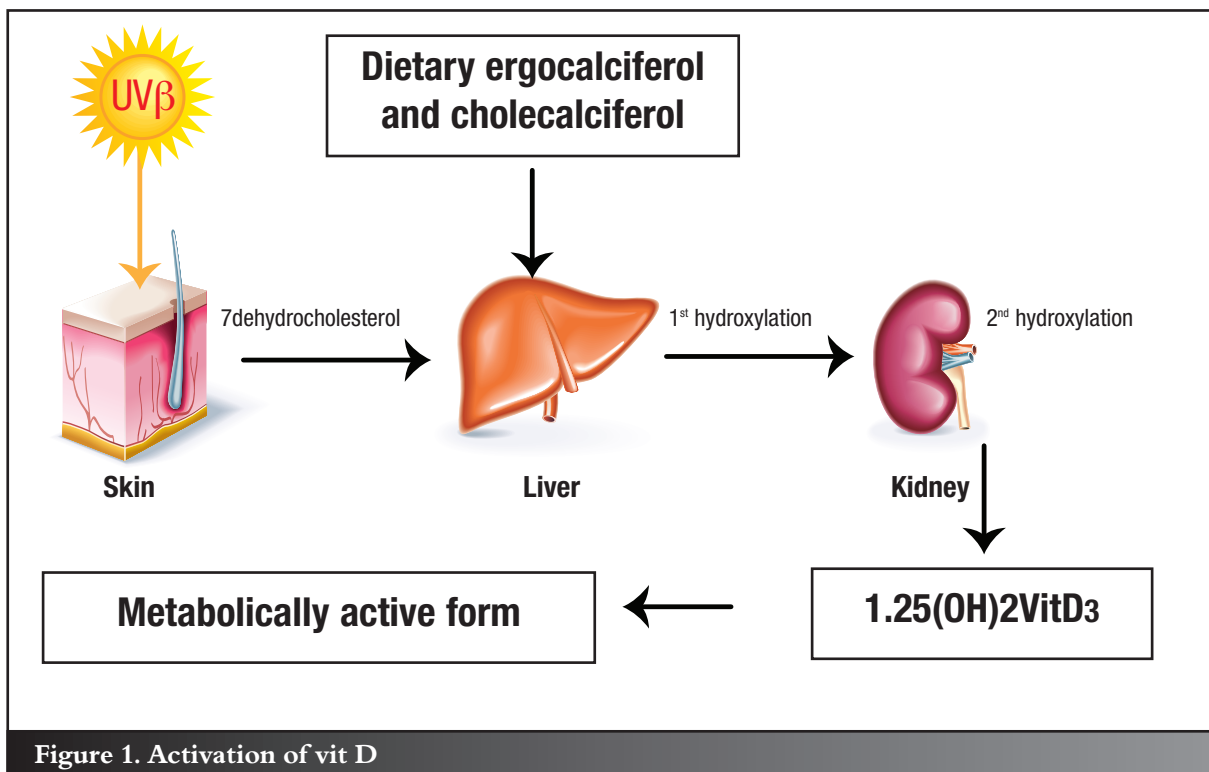


Figure 1. Activation of vit D

The melanin content of the skin is another determinant of the efficiency of the first step in the activation of the biochemical cascade. It has been demonstrated that 18 millijoule UV per cm² lightly pigmented irradiated skin produces the same concentration vit D₃ as 5-10 times more irradiation of a heavily pigmented skin.^{8,9} Melanin pigment is one of the important regulators of vit D activation. This may serve as an explanation for the different susceptibilities for diseases between races as well as the geographic distribution of races, where most of the lighter pigmented races populate the northern hemisphere (UV deficient) and the darker races the tropics where sun exposure is significantly more intense and protection is required in order to prevent over-activation of vit D.

A question arises on whether vit D is indeed classifiable as a vitamin. The generally accepted definition of a vitamin is that it is a chemical substance in food which in minute quantities is essential for metabolism. It is clear that vit D does not fulfil these criteria but rather those for a hormone which is defined as a chemical substance produced in one part of the body and which stimulates functional activity in another.¹⁰ A more intriguing question is how furred and feathered animals activate 7-dehydrocholesterol, where UV is blocked from reaching the skin. It has been demonstrated that vit D is generated in the oily secretions on the fur and feathers, activated by the UV rays of the sun and harvested orally during grooming.¹¹

Research into the biochemical actions of vit D₃ in the human body has been an area of intense interest during the past decade. The list of diseases allegedly associated with vit D deficiency is subsequently rapidly expanding. This comes as no surprise as it has been demonstrated that vit D₃ influences the functions of over 200 genes of the human genome directly, increasing the susceptibility to a wide range of abnormal tissue reactions when deficient. Besides the vit D₃ receptors in the intestine and bone, vit D₃ receptors have been demonstrated in the brain, prostate, breast, colon, cells of the immune system, vascular smooth muscle and cardiac muscle cells.¹²⁻¹⁴ The following brief overview focuses on recent advances and controversies in the study of disease states associated with a vit D deficiency.

Bone health

The role of vit D in the maintenance of the calcium balance of the skeleton is the classical activity which has been researched exhaustively over the past 70 years. The mechanisms entail its promotion of calcium absorption in the intestine and facilitation of proper function of parathyroid hormone thereby maintaining basic metabolic activities requiring adequate serum calcium and phosphate concentrations. The impact of a vit D deficiency is well publicised and manifests as rickets in children and osteomalacia after skeletal growth has ceased. It is not the purpose of this paper to elaborate on skeletal biochemical changes associated with vit D deficiency states and readers are referred to other publications for this purpose.¹⁵

Immune system

Vit D₃ enhances the phagocytic capacity of macrophages through mitochondrial activation. It also stimulates killer T-lymphocytes through the activation of vit D₃ receptors on their cell surfaces thereby improving their antigen neutralising capacity.¹⁶⁻¹⁸ Vit D₃ furthermore increases the production of an antimicrobial peptide, cathelicidin, in response to a microbial trigger.^{18,19} This provides scientific evidence for the successes achieved by Niels Finsen more than 100 years ago in applying phototherapy to patients suffering from smallpox and lupus vulgaris. A lower concentration of vit D₃ due to lack of UV exposure may be one of the reasons for the higher incidence rate of influenza infection during the winter.²⁰ Evidence points to an association between vit D deficiency and multiple sclerosis in women²¹ due to vit D's alleged autoimmune suppressive effect.²² In a study on 206 patients with early inflammatory polyarthritis an inverse relation between 25(OH) vit D concentrations and the Activity Score 28-joint Assessment Scale was found.²³ Preliminary findings on the associations between vit D deficiency and autoimmune diseases like autoimmune interstitial lung disease, lupus and rheumatoid arthritis are promising.²⁴ More research is however required in order to verify the scientific basis of these observations.

Glucose metabolism

In a study of more than 10 000 children, daily vit D supplementation with doses of 2 000 IU was found to be associated with a 78% reduced risk of developing type 1 diabetes compared to supplementation with lower doses.²⁵ A meta-analysis of four studies of a large cohort of children receiving vit D supplementation demonstrated a 29% reduction in the risk for developing type 1 diabetes compared to non-supplemented children.²⁶ A ten-year study of 524 non-diabetic adults demonstrated an inverse relationship between serum 25(OH) vit D concentrations, future hyperglycaemia and insulin resistance.²⁷ The link between hypo-vitaminosis D and adiposity, diabetes and calcified atherosclerotic plaque has recently been demonstrated.²⁸ It may partly be explained by the propensity for vit D to dissolve in body fat, rendering low concentrations of free vit D available for metabolic activation in obese patients.

Cardiovascular disease

A report of the National Health and Nutrition Survey which was based on nearly 5 000 participants, found that low concentrations of 25(OH) vit D were associated with an increased risk for peripheral arterial disease.²⁹ Although still clouded in controversy, several studies demonstrated a link between low 25(OH) vit D concentrations and cardiovascular events in hypertensive patients,¹³ myocardial infarction³⁰ and all-cause cardiovascular mortality.³¹ Knowledge in this field will undoubtedly progress in the near future.

Malignant disease

An increasing number of studies associate vit D deficiency with a higher risk of developing certain malignancies. Analysis of a large number of cases found a significantly lower risk for breast cancer in women with normal serum 25(OH) vit D concentrations.^{32,33} In a separate study, vit D supplementation has been reported to reduce the risk for breast cancer.³⁴ Vit D mediated facilitation of the immune response against transformed cells, the direct binding of vit D to receptor sites on transformed cells or other as yet undisclosed mechanisms may be implicated. Molecular evidence in support of epidemiological studies on large numbers of cancer patients that indicate significant reductions in the risks for colon, ovarian, kidney and breast cancers when normal serum concentrations of 25(OH) vit D is maintained,³⁵ is certain to be an exciting field of research in the future. Not all agree with these preliminary findings and question statistical methodologies, non-randomised patient selection and lack of data as major flaws in some of the reports not cited in this overview. Although population genetics should not be negated, the different risks for the development of malignancies in geographic regions that experience less sun exposure may well be the result of lower population averages of serum 25(OH) vit D concentrations in such regions. It should be cautioned however that there is an undisputed risk for the development of malignancies of the skin with chronic sun and sun-bed exposure³⁶ and as with many other aspects of life, a balanced approach to sun exposure is required in order to remain within safe limits. Before vit D supplementation is universally accepted as a preventative measure for malignant diseases, detailed mapping of the metabolic actions of vit D3 is required.

Normal serum concentrations

Vit D status is assessed by measuring the serum concentration of 25(OH) vit D. The normal concentrations and reference ranges are reflected in *Table I*. An estimated one billion people worldwide do not reach the minimum optimal serum concentration of 30 ng/ml.¹² Vit D supplementation should not be prescribed unless the serum concentration has been found to be deficient or insufficient (*Table I*).

Table I: Serum 25(OH) vit D concentrations in deficiency, insufficiency, sufficiency and toxicity states

Deficiency	< 10 ng/ml	0-25 nmol/l
Insufficiency	10-30 ng/ml	25-75 nmol/l
Sufficiency	30-100 ng/ml	75-250 nmol/l
Toxicity	>100 ng/ml	>250 nmol/l

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Vitamin D-containing food

Although vit D is synthesised and activated in the body as outlined, several external sources are available that would reduce the need for UV activation of 7-dehydrocholesterol in the skin in order to meet the adult requirement of 2 000 IU 25(OH) vit D per day. (Breast-fed infants should receive 400 IU per day until weaned. The same dosage is recommended for children and teens who drink less than 500 ml vit D fortified milk per day.) These recommendations are constantly updated by the Institute of Medicine's Food and Nutrition Board of the USA. The external sources of vit D (cholecalciferol and ergocalciferol) are briefly listed below:³⁷

- Cholecalciferol tablets (available in a wide range of concentrations of up to 50 000 IU per tablet)
- Wild salmon
- Mushrooms (ergocalciferol) particularly those that were exposed to UV
- Mackerel (particularly those that are caught wild. Breeding in captivity reduces its value as a source of vit D)
- Cod liver oil (beware of vit A toxicity)
- Tuna and sardines
- Milk, yogurt, beef or calf liver and egg yolks

Vit D toxicity

Vit D toxicity has not been reported to result from exposure to natural sunlight due to the intricate activation pathway with its negative feedback mechanisms. Vit D toxicity is however theoretically possible by taking chronic daily excessive amounts (in the order of 40 000 IU per day or more⁸) of vit D orally or using UV devices. Little information is however available on the effects (if any) of vit D toxicity. The National Institute of Health set the maximum upper limit of the serum concentration of 25(OH) vit D arbitrarily on 100 ng/ml (*Table I*) and the daily intake on 2 000 IU for adults. This value will undoubtedly be increased as 30 minutes of full body sun exposure is alleged to produce 10 000 IU vit D.³⁷

The content of the article is the sole work of the author. No benefits of any form have been received from a commercial party related directly or indirectly to the subject of this article.

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