**Abstract**

Vitamin D has many physiological functions including upregulation of intestinal calcium and phosphate absorption, mobilization of bone resorption, renal reabsorption of calcium as well as actions on a variety of pleiotropic functions. It is believed that many of the hormonal effects of vitamin D involve a 1,25-dihydroxyvitamin D$_3$-vitamin D receptor-mediated transcriptional mechanism involving binding to the cellular chromatin and regulating hundreds of genes in many tissues. This comprehensive historical review provides a unique perspective of the many steps of the discovery of vitamin D and its deficiency disease, rickets, stretching from 1650 until the present. The overview is divided into four distinct historical phases which cover the major developments in the field and in the process highlighting the: (a) first recognition of rickets or vitamin D deficiency; (b) discovery of the nutritional factor, vitamin D and its chemical structure; (c) elucidation of vitamin D metabolites including the hormonal form, 1,25-dihydroxyvitamin D$_3$; (d) delineation of the vitamin D cellular machinery, functions and vitamin D-related diseases which focused on understanding the mechanism of action of vitamin D in its many target cells.

**Introduction**

The history of vitamin D is a rich and storied subject and is now over 350 years old. It began in the early 1600s with the first descriptions of the human deficiency disease: rickets in children and osteomalacia in adults. Of course, there were no precise medical details that distinguished it from other bone diseases, but treatises describing the symptoms and lithographs from that time showing bone deformities resembling rickets leave little doubt that it was vitamin D deficiency. It took another 250 years to define the cause of vitamin D deficiency in the 1900–1920 period when physicians and biochemists elucidated the role of sunlight and identified the chemical structure of the two main forms of the vitamin D molecule, vitamin D$_2$ and vitamin D$_3$.

Another 50 years elapsed before the metabolism of vitamin D was first described in 1967 and the active form of vitamin D, namely 1,25-dihydroxyvitamin D (1,25-(OH)$_2$D), was discovered. The period of time since has witnessed the exciting realization that vitamin D has its own set of dedicated specialized machinery consisting of transport proteins, metabolic enzymes and vitamin D receptor (VDR) to mediate the actions of vitamin D, not only in bone but also in many other tissues around the body where it has a myriad of different physiological effects.

Before we get into the history of vitamin D, let us first remind the reader of the general aspects of its nomenclature, origins and principal functions. Vitamin D is a steroidal substance required by all vertebrates including humans to maintain blood calcium and phosphate within a narrow normal range and thereby support a healthy skeleton, muscle contraction, immune function and optimal cellular functions in many locations around the body (1). The name vitamin D is a term coined by nutritionists, and...
is not a chemical term, which is defined as ‘a substance with anti-rachitic properties that will cure rickets’. In human biology, vitamin D usually refers to two substances: vitamin D$_3$ (usually known as cholecalciferol) of animal origin and vitamin D$_2$ (referred to as ergocalciferol) of plant or fungal origin. These two forms have roughly equal potencies, similar metabolic patterns and identical effects in the body.

Because of the four phases of vitamin D history, this review is divided into four sections each summarizing one particular time period:

1. 1650–1890: history of vitamin D deficiency (rickets)
2. 1890–1930: history of the discovery of vitamin D and its structural elucidation
3. 1930–1975: history of the discovery of vitamin D metabolites including 1,25-(OH)$_2$D$_3$
4. 1975–present: history of the discovery of the vitamin D cellular machinery, functions and vitamin D-related human diseases.

Since the different facets of the history of vitamin D represent interesting topics and span many centuries, they have been reviewed by many previous historians, including the current author, and interested readers are invited to further access these because they focus on different aspects of the overall story (2, 3, 4, 5, 6, 7, 8).

1650–1890: history of vitamin D deficiency (rickets)

There is no doubt that rickets was prevalent in Europe long before it was recognized as a specific disease in the 15th century, but the earliest documentation of the word ‘rickets’ was in a domestic receipt book of an English family in 1632 and the earliest printed record of rickets as a disease causing death in the London Bill of Mortality in 1634 (reviewed by (2, 3, 4)). The term rickets is thought to have its origins in the verb in the Dorset dialect to ‘rucket’, which means to breathe with difficulty. However, some claim the term rickets is derived from the Anglo-Saxon word ‘wrikken,’ meaning to twist. Rickets and osteomalacia were first clearly described by Daniel Whistler in the Netherlands (1645) as a condition in which the skeleton was poorly mineralized and deformed (9). Francis Glisson (1650) provided the first documented records with his book entitled De Rachitide first published in Latin in 1650 and then translated into English in 1671 (10). It features a lithograph of children with bowing of the legs and skeletal deformities which are the hallmarks of vitamin D deficiency. One of those Glisson lithographs was reproduced as a frontispiece in a landmark treatise on Rickets Including Osteomalacia and Tetany by AF Hess in 1929 (11). It is reproduced here as Fig. 1.

A more recent definition of vitamin D deficiency has grown to include defective chondrocyte differentiation and lack of mineralization of the growth plate, but the common feature of vitamin D deficiency is insufficiently mineralized or calcified bone matrix (1, 12, 13). Rickets is characterized by a deformed and misshaped skeleton, particularly bending and bowing of the long bones and enlargement of the epiphyses of the joints of the rib cage,
arms, legs and neck. Victims have painful movements of the rib cage and difficult breathing. In China, medical texts refer to deformities of the rib cage in severe rickets as ‘chicken breast’ (5). Severe rickets is often accompanied by pneumonia. The loss of the important role of vitamin D in strengthening the immune system compounds this problem. Though rarely is rickets life-threatening, it certainly lowers the quality of life for the afflicted individual and leads to secondary problems. One of these secondary effects of rickets occurs in young women who had vitamin D deficiency in childhood causing deformities of the pelvis which result in difficulties in childbirth (14). Shorter (14) speculates that rickets in early life must have resulted in numerous deaths of women during their first delivery.

Vitamin D deficiency is partly the result of inadequate skin synthesis of vitamin D₃ from 7-dehydrocholesterol compounded by a low dietary intake of vitamin D₂ from plant or fungal sources or vitamin D₃ from animal products. The advent of the Industrial Revolution in Western Europe heralded in massive air pollution in the form of smoke from mills and burning of fossil fuels. This dramatically reduced the amount of UV light reaching the ground. Since the workers needed for these new industrial jobs were required to move from their rural locations into dingy, poorly-lit cities, their exposure to UV light diminished and skin synthesis of vitamin D was reduced. Rickets resulted and was associated with lack of exposure to sufficient sunlight. Thus, the 18th and 19th centuries saw a higher increase in rickets in the industrialized cities of northern Europe. The Dickensian character Tiny Tim, of the novel A Christmas Carol, clearly represents a child with a deformed skeleton who must have been a common sight in the dark cities of the late 19th century (7). Rickets was particularly prevalent in the industrialized Britain of the 16th–20th centuries, and thus, it is no surprise that it was referred to in old texts as ‘the English disease’ (7, 15).

Despite the fact that rickets seemed to be associated with lack of exposure to sunlight, by the late 1700s, some, including Percival (16) in the UK, were advocating the use of cod liver oil for the treatment of rickets suggesting a nutritional aspect to vitamin D. In contrast, in the early 1800s, Sniadecki (17) in Poland was documenting the differential incidence in city-dwellers and rural-dwellers suggesting some environmental factor was involved. He speculated that sunlight or fresh air might be involved in the etiology of the disease. By the end of the 19th century, a rigorous debate roared on whether rickets was caused by the lack of some dietary substance or an environmental factor and how could these two points of view be reconciled.

1890–1930: history of the discovery of vitamin D and its structural elucidation

By the 1890s, some researchers such as Owen (18) and Palm (19), who clearly supported the environmental theory, produced evidence that there were big geographical differences in the incidence of rickets in different parts of the UK and northern and southern China. Palm, a medical missionary, went on to suggest that exposure of children to sunlight would cure rickets (19). Subsequently, researchers in Europe and the United States namely Buchholtz (1904), Raczynski (1913), Huldshinsky (1919), and later Chick (1922) and Hess & Weinstock (1924) performed experiments in which laboratory animals and children with rickets could be cured with sunlight or light from mercury arc lamps (7, 20, 21, 22, 23, 24). This clearly demonstrated that lack of exposure to UV light was one cause of rickets.

But the proponents of the theory that a dietary factor could also be involved continued with their experiments too. The early 20th century was a momentous period in nutritional research in which nutritionists showed that a diet of highly purified carbohydrates, protein, fat and salt is unable to fully support growth and life of experimental animals (25). By adding various ‘trace factors’, researchers were able to restore growth and a full range of physiological actions. The first of these trace factors was thiamin discovered by Funk (26) which cured neuritis in what Funk termed the ‘vital amine or vitamin theory.’ Thiamin was later renamed vitamin B₁, but it was one of a number of vitamin substances that are defined as ‘trace compounds which are derived from the diet and are required in small amounts per day and perform an essential role critical to life.’ Vitamin D was identified as one of these substances playing a critical role in skeletal growth and calcium and phosphate homeostasis. However, strictly speaking, vitamin D has been misnamed since it can also be derived from exposure to UV light and is not required to be in the diet. In practise and for a variety of social and religious reasons, many populations around the world do not receive adequate UV light, especially during the winter months, so that a dietary intake is essential.

The discovery of the nutritional factor, later termed vitamin D by McCollum (27), came largely as the result of the work of a number of researchers: Mellanby, McCollum, Steenbock and Hart working independently. Sir Edward Mellanby (28) in the UK reasoned that rickets might be due to a dietary deficiency and managed to produce beagle dogs with severe rickets by feeding them oatmeal and then cured their rickets with cod liver oil. Since cod liver oil is a mixture of lipids and a rich source of vitamin A, it was not clear what the active ingredient might be. McCollum (29),
working first at the U Wisconsin and then Johns-Hopkins, heated and bubbled oxygen through the cod liver oil to destroy the vitamin A and found that the product still cured rickets. Building on the new vitamin nomenclature, he termed the new substance vitamin D. But how was the field to reconcile the apparently unconnected findings that UV light and a nutritional substance termed vitamin D could both cure rickets? Harry Steenbock also working at the U Wisconsin-Madison performed the definitive experiment. Steenbock & Black experimented with the diets of goats and found that sunlight or UV irradiation of the animals or their diets resulted in rickets being cured in the goats (30). Steenbock traced the bioactive substance in irradiated food to the non-saponifiable fraction of lipids in the diet and showed that it cured rickets (31). Dietary vitamin D was born.

Subsequently, Steenbock was able to show that irradiated yeast contained significant amounts of vitamin D, later shown to be vitamin D$_3$ and that the yeast could be irradiated and added to milk which formed the basis of the first food fortification with vitamin D (5). Though Steenbock and the University of Wisconsin filed a patent for milk fortification with vitamin D, the proceeds from this discovery were used to establish the Wisconsin Alumni Research Foundation (WARF) which was one of the prototypical organizations intended to allow universities to plough the benefits of their research into future research. WARF funded the research of a number of scientists inside and outside of the vitamin D field, included several Nobel laureates, with the proceeds of Steenbock's patent. Furthermore, vitamin D fortification of a variety of foodstuffs (including milk, margarine, bread and even beer) has become a major nutritional tool in the fight to prevent rickets and osteomalacia around the world (5).

In the late 1920s, Windaus and colleagues (32) isolated the key anti-rachitic substance from a mixture of irradiated plant sterols and named it vitamin D$_1$, although they did not identify its structure. Later, vitamin D$_1$ was shown to be a mixture of vitamin D$_2$ and tachysterol. A British group headed by Askew (33) successfully identified and determined the structure of the anti-rachitic, plant-derived sterol as vitamin D$_2$ or ergocalciferol. Windaus's group confirmed the structure of vitamin D$_2$ (34) and also isolated and identified the animal-derived, anti-rachitic vitamin D$_3$ or cholecalciferol and its skin precursor, 7-dehydrocholesterol (35). For his discovery of the structures of vitamin D$_3$, 7-dehydrocholesterol and several other sterols, Adolf Windaus was awarded the 1928 Nobel Prize for Chemistry (Fig. 2).

**1930–1975: history of the discovery of vitamin D metabolites including 1,25-(OH)$_2$D$_3$**

Chemically synthesized vitamin D$_2$ and vitamin D$_3$ have been available since the 1930s and paved the way for the study of their biological functions and metabolism. The physiological roles of vitamin D are primarily its roles in calcium and phosphate homeostasis (1) and include:

1. stimulation of intestinal calcium and phosphate absorption;
2. mobilization of calcium from bone;
3. renal reabsorption of calcium.

All three of these functions serve to raise blood calcium and phosphate and ensure that these ions are available to ensure health and prevent rickets. Elucidating the details of these physiological functions became the main foci during the 1930–1960 time period, and research revealed that vitamin D was intimately connected to the roles of other calcium and phosphate-related hormones including parathyroid hormone (PTH) and calcitonin. Details of these connections are beyond the scope of this chapter and are described in reviews (1) and in other articles in this special series.

In the 1960s, there was considerable debate over whether the functions of vitamin D were carried out by vitamin D itself or its possible metabolites. Consequently, intense effort was put into studying the metabolism of vitamin D by using chemically synthesized radioactive versions of vitamin D$_2$ and vitamin D$_3$. The pioneer in this area was Egon Kodicek at the Dunn Nutritional Laboratories, U Cambridge UK. After 10 years of work, Kodicek (36) concluded that vitamin D was active without...
Table 1  History of the discovery of the major metabolites of vitamins D$_2$ and D$_3$.

| Metabolite                  | Tissue source | Biosynthetic enzyme                      | Biological role                        | Discovery                          |
|-----------------------------|---------------|------------------------------------------|----------------------------------------|------------------------------------|
| Vitamin D$_2$ metabolites   |               |                                          |                                        |                                    |
| 25-OH-D$_3$                 | Liver         | 25-Hydroxylase (CYP2R1)                  | Main circulating metabolite            | Blunt et al. 1968 (38)             |
| 1,25-(OH)$_2$D$_3$          | Kidney (major) | 1α-Hydroxylase (CYP27B1)                 | Active hormonal form                   | Lawson et al. 1969 (39)           |
| 24,25-(OH)$_2$D$_3$         | Kidney (major) | 24-Hydroxylase (CYP24A1)                 | Principal catabolite                   | Myrtle et al. 1970 (40)           |
| 25,26-(OH)$_2$D$_3$         | Unknown       | 26-Hydroxylase (?)                       | Catabolite                             | Holick et al. 1971 (41)           |
| 25-OH-D$_2$26,23-lactone    | Kidney (major) | 24-Hydroxylase (CYP24A1)                 | Presumed catabolite                    | Suda et al. 1970a (48)            |
| 1,24,25-(OH)$_3$D$_3$       | Kidney (major) | 24-Hydroxylase (CYP24A1)                 | Unknown possible catabolite            | Suda et al. 1970b (50)            |
| Calcioc acid                | Kidney (major) | 24-Hydroxylase (CYP24A1)                 | Excretory form                         | Wichmann et al. 1979 (51)        |
| Calcioc acid                | Kidney (major) | General cytochrome P450 (CYP3A4)         | Excretory form                         | Esvelt et al. 1981 (53)           |
| 4α,25-(OH)$_2$D$_3$         | Liver         | 24-Hydroxylase (CYP24A1)                 | Excretory form                         | Kaufmann et al. 2019 (76)         |
| 4β,25-(OH)$_2$D$_3$         | Liver         | 24-Hydroxylase (CYP24A1)                 | Excretory form                         | Wang et al. 2013 (77)             |
| Vitamin D$_3$ metabolites   |               |                                          |                                        |                                    |
| 25-OH-D$_3$                 | Liver         | 25-Hydroxylase (CYP2R1)                  | Main circulating metabolite            | Suda et al. 1969 (45)             |
| 1,25-(OH)$_2$D$_3$          | Kidney (major) | 1α-Hydroxylase (CYP27B1)                 | Active hormonal form                   | Jones et al. 1975 (46)           |
| 24,25-(OH)$_2$D$_3$         | Kidney (major) | 24-Hydroxylase (CYP24A1)                 | Principal catabolite                   | Jones et al. 1980 (47)           |
| 1,24,25-(OH)$_3$D$_3$       | Kidney (major) | 24-Hydroxylase (CYP24A1)                 | Presumed catabolite                    | Reddy et al. 1986 (78)           |

being metabolized. In retrospect, the radioactive vitamin D that his group were using was insufficiently labeled to detect its metabolites. However, Hector DeLuca, again at the U Wisconsin-Madison, and the final graduate student of Harry Steenbock, synthesized radioactive vitamin D$_3$ with much higher specific activity (37) and was able to demonstrate metabolism to more polar metabolites, the principal one being 25-hydroxyvitamin D$_3$ (25-OH-D$_3$) (38) made in the liver and the first identified natural vitamin D metabolite.

25-OH-D$_3$ proved to be more potent biologically than vitamin D$_3$ and was present in the bloodstream at a higher concentration (38). We now identify 25-OH-D$_3$ as the principal circulating form of vitamin D. But that is not the extent of vitamin D metabolism. Several other groups then entered or re-entered the picture, including Dr Kodicek’s, as well as that of one of Dr DeLuca’s former graduate students Dr Anthony Norman. Among the other polar products of vitamin D$_3$ was a metabolite even more potent than 25-OH-D$_3$, namely 1α,25-dihydroxyvitamin D$_3$ (1,25-(OH)$_2$D$_3$) which is now universally accepted as the hormonal form of vitamin D$_3$. Several groups including Dr Kodicek’s, Dr Norman’s and Dr DeLuca’s were credited with playing a role in the discovery and/or

Figure 3  Metabolism and mechanism of action of vitamin D$_3$. Skin-synthesized or dietary vitamin D$_3$ is converted via a two-step hydroxylation process into the active hormonal form 1,25-(OH)$_2$D$_3$. The hormone binds to the vitamin D receptor (VDR) and regulates serum calcium ($s$Ca$^{++}$) and serum phosphate ($s$PO$_4^{2-}$) levels ensuring sufficient minerals for normal cellular activity around the body including bone. Insufficient vitamin D results in insufficient 1,25-(OH)$_2$D$_3$ and vitamin deficiency rickets. Circled in red are the proteins in the vitamin D-specific machinery that when mutated also result in some type of rickets. Circled in blue is the enzyme CYP24A1 that when mutated results in elevated 1,25-(OH)$_2$D$_3$ and hypercalcemia and/or kidney stones.
in the structural identification of 1,25-(OH)\(_2\)D\(_3\). Kodicek’s group administered a mixture of radioactive \([4-\text{H}]\) and \([1-\text{H}]\) vitamin D\(_3\) preparations and showed that one polar metabolite lost its tritium atom during metabolism that aided in its identification as a 1-hydroxylated compound (39). Furthermore, the Cambridge group also showed that the hormone was biologically generated in the kidney (39, 42). Dr Norman’s group showed that the new metabolite was associated with the chromatin of intestinal mucosal cells and had greater biological activity than even 25-OH-D\(_3\) (40). Holick et al. (41) showed that the additional 1-hydroxyl group was in the 1\(\alpha\) orientation and supported their identification of the metabolite as 1\(\alpha\),25-(OH)\(_2\)D\(_3\) with mass spectrometry. Chemically synthesized 1,25-(OH)\(_2\)D\(_3\) was first produced by Semmler et al. (43) and made commercially by a group headed by Dr Milan Uskokovic at Hoffmann-La Roche in the early 1970s and is known clinically by the name calcitriol (44).

The identification of the principal metabolites, 25-OH-D\(_3\) and 1,25-(OH)\(_2\)D\(_3\), spawned a frenzy of research activity in the vitamin D area and the discovery of a number of other vitamin D metabolites (1). Among these are the principal metabolites of vitamin D\(_2\) including 25-OH-D\(_2\) (45), 1,25-(OH)\(_2\)D\(_2\) (46) and 24,25-(OH)\(_2\)D\(_2\) (47). Also identified in that mixture of metabolites arising from radioactive vitamin D\(_3\) were several compounds that are presumed to be inactive catabolites including, 24,25-(OH)\(_2\)D\(_3\), 25,26-(OH)\(_2\)D\(_3\), 25-OH-D\(_3\)-26,23-lactone, 1,24,25-(OH)\(_3\)D\(_3\) and calcitroic acid (48, 49, 50, 51, 52, 53).

A summary of the main metabolites of both vitamin D\(_3\) and vitamin D\(_2\) along with their tissue source, biosynthetic enzyme, details of first reporting and biological role is presented in Table 1 and depicted in a metabolic pathway diagram (Fig. 3).

1975–present: history of the discovery of the vitamin D cellular machinery, functions and vitamin D-related human diseases

The discovery of the active forms of vitamin D heralded in a search for

(a) the signal transduction mechanisms to explain how 1,25-(OH)\(_2\)D\(_3\) was able to produce its various biological effects;
(b) identification of the enzymes responsible for the synthesis and catabolism of 1,25-(OH)\(_2\)D\(_3\);
(c) a clear understanding of the regulation of the vitamin D endocrine system.

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**Table 2**

| Protein | Abbreviation | Function |
|---------|--------------|----------|
| vitamin D-binding globulin | DBP | Transport of vitamin D and its metabolites |
| vitamin D receptor | VDR | Regulation of vitamin D-dependent genes |
| 25-Hydroxyvitamin D-24-hydroxylase | CYP27B1 | 25-hydroxylation of vitamins D\(_2\) and D\(_3\), 1\(\alpha\)-hydroxylation of 25-OH-D\(_2\) and 25-OH-D\(_3\) |
| 1\(\alpha\)-Hydroxylase | CYP2R1 | 1\(\alpha\)-hydroxylation of 25-OH-D\(_2\) and 25-OH-D\(_3\) |
| 24-Hydroxylase | CYP24A1 | Complete catabolism of vitamin D |

*The specific vitamin D signal transduction machinery is specialized to transport, activate, mediate the biological effects of and catabolize vitamin D.

**Biological function**
- Transport of vitamin D and its metabolites
- Regulation of vitamin D-dependent genes
- Complete catabolism of vitamin D
- Other cellular proteins play a general role in vitamin D metabolism and action, for example, CYP3A4 but this degrades many other molecules and drugs.

**Discovery**
- 1975 (64) Brumbaugh et al.
- 1991 (79) McDonnell et al.
- 1975 (55) et al.
- 2003 (81) et al.
- 1997 (75) et al.
- 1997 (70) Takeyama et al.
- 1997 (71) Ohyama & Okuda

**Abbreviation**
- DBP: vitamin D-binding globulin
- VDR: vitamin D receptor
- CYP27B1: 25-hydroxylase
- CYP2R1: 1\(\alpha\)-Hydroxylase
- CYP24A1: 24-Hydroxylase

**Tissue location or source**
- Liver
- Kidney
- Extra-renal sites

**Protein**
- vitamin D-binding globulin
- vitamin D receptor
- 25-Hydroxyvitamin D-24-hydroxylase
- 1\(\alpha\)-Hydroxylase
- 24-Hydroxylase

**Gene cloning**
- Fraser
- Cooke
- Cheng
- Haussler 1969
- St-Arnaud

**Regulation of vitamin D-dependent genes**
- Cooke
- Cheng
- Haussler 1969
The cytochrome P450-containing enzymes (CYPs) responsible for vitamin D metabolism were first studied in the early 1970s in tissue extracts of liver and kidney (67, 68, 69) and then in tissue culture and given names based upon their hydroxylation activity: 25-hydroxylase, 1α-hydroxylase and 24-hydroxylase. In the early 1990–2005 period, all three enzymes were purified, cloned and expressed in cell culture systems, principally by Canadian group of St-Arnaud (70) as well as the Japanese groups of Kato S (71), Okuda (72) and Sakaki (73, 74) as well as Russell’s group at the U Texas (75). The three enzymes are now known as CYP2R1, CYP27B1 and CYP24A1. A review of the CYP field and how these enzymes operate and how they are regulated is provided (66). A summary of the history of the signal transduction protein machinery for vitamin D including VDR, DBP and the various CYPs is provided in Table 2.

No review of the recent history of vitamin D would be complete without an overview of how defects in vitamin D metabolism result in human disease. It is now evident that vitamin D deficiency and rickets are caused by several genetic and acquired errors in vitamin D metabolism which involve any of the major protein components of the vitamin, vitamin D requires a protein to transport it around the body and the vitamin D-binding globulin (usually abbreviated as DBP) performs this function. DBP was first identified as Gc (group-specific component) in the 1970s, and its properties have been reviewed extensively by the father figure of the field Roger Bouillon, U Leuven, Belgium (65). DBP has a high affinity for most of the main metabolites of vitamin D, most notably 25-OH-D, and because of this, 25-OH-D is the main circulating form in the blood.

Table 3  History of the main vitamin D-related genetic and acquired human diseases and animal models generated to study them.

| Disease                                | Cause                                   | Initial report       | Animal model equivalent      | Generated by                        |
|----------------------------------------|-----------------------------------------|----------------------|-----------------------------|-------------------------------------|
| Vitamin D deficiency rickets           | Lack of dietary vitamin D               | F Glisson 1671 (10)  | Beagle dog on oatmeal diet  | Mellanby 1919 (28)                  |
| Vitamin D dependency rickets type 1A   | Lack of skin synthesis of D             | Fraser et al. 1972   | CYP27B1 null mouse          | Kato 1999 (83)                       |
| Vitamin D dependency rickets type 1B   | Genetic defect in CYP27B1               | Cheng et al. 2004    | CYP2R1 null mouse           | Panda et al. 2001 (84)              |
| Vitamin D dependency rickets type 2    | Genetic defect in CYP2R1                | Rosen et al. 1979    | VDR null mouse              | St-Arnaud et al. 2003 (85)          |
| Idiopathic infantile hypercalcemia     | Genetic defect in VDR                  | Lightwood 1953      | CYP24A1 null mouse          | Zhu et al. 2013 (86)                |
| Chronic kidney disease                 | Loss of Kidney CYP27B1 enzyme activity  | Schlingmann et al. 2011 | Dog nephrectomy models      | Yoshizawa et al. 1997 (89)         |
|                                        |                                         | DeLuca & Avioli 1970 |                                             | Li et al. 1998 (90)                |
|                                        |                                         | Brickman et al. 1974 |                                             | St-Arnaud et al. 2000 (93)         |
|                                        |                                         |                      |                                             | Rutherford et al. 1977 (96)        |

These studies began almost as soon as metabolism was recognized in the late 1960s when Mark Haussler, in AW Norman’s laboratory, demonstrated that vitamin D metabolites were associated with the chromatin (54). Clear evidence of the protein that is now termed the vitamin D receptor (VDR) was produced by Haussler’s lab (55). The VDR protein from various species was later purified and its gene was cloned by Haussler’s group (56, 57). Study of the pure protein has led to a determination of its crystal structure (58). Parallel to these investigations of the VDR have come other studies on how it works both at the whole-body level in calcium and phosphate homeostasis and other pleiotropic functions (1, 8, 59) and at the cellular level in a classic steroid hormone super-family like process through a transcriptional mechanism (60). Over the past 30 years, Mark Haussler, Wes Pike and colleagues (61) have demonstrated that 1,25-(OH)₂D₃ works through a VDR-mediated mechanism that involves many coactivators and repressors to directly interact with and regulate hundreds of genes around the body. Other researchers, most notably Anthony Norman (62), have proposed that some of the actions of vitamin D occur through rapid non-genomic signaling pathways, possibly involving a plasma membrane VDR but this protein has never been fully characterized at the molecular level. Nevertheless, there remains some uncertainty that all vitamin D ligands and analogs produce their effects through a genomic VDR mechanism (63).

The history of two other components of the vitamin D machinery deserves some mention.

These are vitamin D-binding globulin (64, 65) and the cytochromes P450-containing enzymes that metabolize vitamin D into its many metabolites (66). Being a fat-soluble vitamin, vitamin D requires a protein to transport it around the body and the vitamin D-binding globulin (usually abbreviated as DBP) performs this function. DBP was first identified as Gc (group-specific component) in the 1970s, and its properties have been reviewed extensively by the father figure of the field Roger Bouillon, U Leuven, Belgium (65). DBP has a high affinity for most of the main metabolites of vitamin D, most notably 25-OH-D, and because of this, 25-OH-D is the main circulating form in the blood.
vitamin D machinery described above. These are compiled into Table 3 where we document the disease name, the component of the vitamin D machinery affected, as well as the publication first describing it. Besides diseases involving too little 1,25-(OH)_{2}D_{3} and resulting in rickets, diseases involving too much 1,25-(OH)_{2}D_{3} which cause hypercalcemia are also included in Table 3. Most of these diseases involving a shortage of 1,25-(OH)_{2}D_{3} are now treated with vitamin D analogs which were developed from knowledge of the metabolism and biological actions of vitamin D. Currently approved and marketed vitamin D analogs are listed in Table 4 along with their original publications.

Conclusions

The history of vitamin D is indeed a rich subject which has already stretched over 350 years and involved the four phases described in this review. While the chemical entity vitamin D remained unknown for all but 100 of those years, the significant medical consequences of vitamin D deficiency were evident for the whole of that time. Many physicians, nutritionists, biochemists, chemists and molecular biologists have worked to elucidate our current knowledge of the nature of vitamin D in addition to its metabolism, mechanism of action and biological activities. That knowledge has paid dividends by providing new therapies for the treatment of deficiency and excess vitamin D action. The field of vitamin D research is arguably one of the highlights of modern medicine.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Table 4

| Vitamin D Analog | Drug name | Marketed by | Field of use* | Initial report |
|-----------------|-----------|-------------|---------------|---------------|
| 25-OH-D_{3}     | Calderol | Organon     | Vitamin deficiency | Blunt & DeLuca 1969 (97) |
| 1,25-(OH)_{2}D_{3} | Calcijex | Genzyme/Sanofi | Chronic kidney disease | Semmler et al. 1972 (43) |
| 1α-OH-D_{3}     | Alfacalcidol | Leo Pharma | Vitamin D dependency type 1A | Barton et al. 1973 (98) |
| 1α-OH-D_{2}     | Doxercalciferol | Genzyme/Sanofi | Chronic kideny disease | Blunt & DeLuca 1969 (97) |
| 19-nor-1,25-(OH)_{2}D_{2} | Calcitriol | Abbott | Chronic kidney disease | Takahashi F et al. 1997 (101) |

*Many of the vitamin D drugs used in chronic kidney disease stages 3–4 and beyond are used to suppress secondary hyperparathyroidism, as well as having a moderate serum calcium-raising activity.
References

1. Jones G, Strugnell SA & DeLuca HE. Current understanding of the molecular actions of vitamin D. Physiological Reviews 1998 78 1193–1231. (https://doi.org/10.1152/physrev.1998.78.4.1193)
2. Swinburne LM. Rickets and the Fairfax family receipt books. Journal of the Royal Society of Medicine 2006 99 391–395. (https://doi.org/10.1258/jrsm.99.8.391)
3. O’Riordan JL & Bijvoet OL. Rickets before the discovery of vitamin D. BoneKey Reports 2014 3 478. (https://doi.org/10.1038/bonekey.2013.212)
4. Mays S. The epidemiology of rickets in the 17th–19th centuries: some contributions from documentary sources and their value to palaeopathologists. International Journal of Paleopathology 2018 23 88–95. (https://doi.org/10.1016/j.ijpae.2017.10.001)
5. Jones G. Vitamin D in The Cambridge World History of Food. Part IVA: The Nutrients- Deficiencies, Surfeits and Food-Related Disorders, pp. 763–768. Eds KF Kiple & KC Ornelas. Cambridge: University of Cambridge Press, 2000.
6. Jones G. The discovery and the synthesis of the nutritional factor vitamin D. International Journal of Paleopathology 2018 23 96–99. (https://doi.org/10.1016/j.ijpae.2018.01.002)
7. Chesney RW. Theobald Palm and his remarkable observation: how the sunshine vitamin came to be recognized. Nutrients 2012 4 42–51. (https://doi.org/10.3390/nu4010042)
8. DeLuca HF. Historical overview of vitamin D. In Vitamin D, 3rd ed., chapter 1, pp. 2–12. Eds D Feldman, JW Pike & JS Adams. Academic Press, 2011.
9. Whistler D, De Morbo Puerili Anglorum, Quem Patrio Idiomate Indigenae Vocant. The Rickets. MD Thesis. Leiden, Netherlands: University of Leiden, 1645.
10. Glisson E. De Rachitide Sive Morbo Puerili Quoi Vulgo. The Rickets Dicitur Indigenae Vocant. The Rickets. MD Thesis. Leiden, Netherlands: University of Leiden, 1645.
11. Hess AE. Frontispiece. In Rickets Including Osteomalacia and Tetany, Philadelphia: Lea & Febiger, 1929.
12. Pettitfoot JM. Nutritional rickets: deficiency of vitamin D, calcium, or both? American Journal of Clinical Nutrition 2004 80 1725S–1729S. (https://doi.org/10.1093/ajcn/80.6.1725S)
13. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughal MZ, Makitie O, et al. Global consensus recommendations on prevention and management of nutritional rickets. Journal of Clinical Endocrinology and Metabolism 2016 101 394–415. (https://doi.org/10.1210/jc.2015-2175)
14. Shorter E. A History of Women's Bodies New York, pp. 1–39. New York: Perseus Books, 1982.
15. Belton N. Not only the English disease. Acta Paediatrica Scandinavia 1986 32 68–75.
16. Percival T. Essays Medical, Philosophical and Experimental on the Medical Use of Cod-Liver Oil, vol. 2. London, 1789.
17. Sniadecki J. Jerdrzej Sniadecki (1768–1838) on the cure of rickets. Proceedings of the Fourth International Congress of Biochemistry, vol. 11, pp. 198–208. Eds W Umbreit, H Molitor & L Pergammon. London: Pergammon, 1960.
18. Osten I. Geographical distribution of rickets, acute and subacute rheumatism, chorea, cancer and urinary calculus in the British Islands. BMJ 1889 1 113–118.
19. Palm TA. The geographical distribution and etiology of rickets. Practitioner 1890 45 270–279.
20. Buchholz E. Ueber Lichtbehandlung der Rachitis und anderer Kinderkrankeiten. In Verhandlungen der Gesellschaft fur der Abteilung fur Kinderheilkunde der 76, vol. 21, p. 116. Breslau, Germany: Versammlung der Gesellschaft Deutscher Naturforcher und Aerzte in Breslau, 1904.
21. Racyński J. Recherches experimentales sur la manque d’action du soleil comme cause de rachitisme. In Comptes Rendus de l’Association de Pediatrics Paris, pp. 308–309, 1913.
42 Fraser DR & Kodicek E. Unique biosynthesis by kidney of a biologically active vitamin D metabolite. Nature 1970 228 764–766. (https://doi.org/10.1038/228764a0)

43 Semmler EJ, Holick MF, Schnoes HK & DeLuca HE. The synthesis of 1,25-dihydroxycholecalciferol – a metabolically active form of vitamin D$_2$. Tetrahedron Letters 1972 40 4147–4150.

44 Baggiolini EG, Wovkulich PM, Iacobelli JA, Hennessy BM & Semmler EJ. Unique biosynthesis by kidney of a biologically active metabolite of vitamin D$_3$. Endocrinology 1973 90 2076–2080. (https://doi.org/10.1210/jem.90.6.2076)

45 Jones G, Schnoes HK & DeLuca HE. Isolation and identification of 1,25-dihydroxyvitamin D$_3$. Biochemistry 1975 14 1250–1256. (https://doi.org/10.1021/bi00767a025)

46 Jones G, Schnoes HK, Levan L & Deluca HF. Isolation and identification of 25-hydroxycholecalciferol: a metabolite of vitamin D$_3$ preferentially active on bone. Biochemistry 1970 9 2971–2972. (https://doi.org/10.1021/bi00816a025)

47 Holick MF, Schnoes HK, DeLuca HE, Gray RW, Boyle IT & Suda T. Isolation and identification of 24,25-dihydroxyvitamin D$_3$, a metabolite of vitamin D$_3$ made in the kidney. Biochemistry 1972 11 4251–4255. (https://doi.org/10.1021/bi00773a009)

48 DeLuca HF, Suda T, Schnoes HK, Ponchon G, Tanaka Y & Holick MF. 25,26-Dihydroxycholecalciferol, a metabolite of vitamin D$_3$ with intestinal calcium transport activity. Biochemistry 1970 9 4776–4780. (https://doi.org/10.1021/bi00826a022)

49 Wichmann JK, DeLuca HF, Schnoes HK, Horst RL, Shepard RM & Jorgensen NA. 25-Hydroxyvitamin D$_3$, 26,23-lactone: a new in vivo metabolite of vitamin D$_3$. Biochemistry 1979 18 4775–4780. (https://doi.org/10.1021/bi00859a002)

50 Holick MF, Klein-Bossaller A, Schnoes HK, Kasten PM, Boyle IT & DeLuca HF. 1,24,25-Trihydroxyvitamin D$_3$. A metabolite of vitamin D$_3$ effective on intestine. Journal of Biological Chemistry 1973 248 6991–6996. (https://doi.org/10.1021/bi00125s000)

51 Eielit RP, Schnoes HK & DeLuca HE. Isolation and characterization of 1-alpha-hydroxy-23-carboxytetranorvitamin D$_3$: a major metabolite of 1,25-dihydroxyvitamin D$_3$. Biochemistry 1979 18 3977–3983. (https://doi.org/10.1021/bi00858a021)

52 Haussler MR, Myrtle JE & Norman AW. The association of a metabolite of vitamin D$_3$ with intestinal mucosa chromatin in vivo. Journal of Biological Chemistry 1968 243 4055–4064. (https://doi.org/10.1016/S0021-9258(19)3278-3)

53 Brumbaugh PF & Haussler MR. Specific binding of 1alpha,25-dihydroxycholecalciferol to nuclear components of chick intestine. Journal of Biological Chemistry 1975 250 1588–1594. (https://doi.org/10.1021/bi02012s004)

54 Middaugh DR, Mangelsdorf DJ, Pike JW, Haussler MR & O’Malley BW. Molecular cloning of complementary DNA encoding the avian receptor for vitamin D. Science 1987 235 1214–1217. (https://doi.org/10.1126/science.3029866)

55 Baker AR, Middaugh DR, Hughes M, Crisp TM, Mangelsdorf DJ, Haussler MR, Pike JW, Shine J & O’Malley BW. Cloning and expression of the chick vitamin D receptor cDNA encoding an avian vitamin D receptor. Molec. Endocrinol. 1988 2 3294–3298. (https://doi.org/10.1210/men.2.10.3294)

56 Bocher AR, Middaugh DR, Hughes M, Crisp TM, Mangelsdorf DJ, Haussler MR, Pike JW, Shine J & O’Malley BW. Cloning and expression of the chick vitamin D receptor cDNA encoding an avian vitamin D receptor. Molec. Endocrinol. 1988 2 3294–3298. (https://doi.org/10.1210/men.2.10.3294)
76 Kaufman M, Martineau C, Arabian A, Traynor M, St-Arnaud R & Jones G. Calcioc acid: in vivo detection and quantification of the terminal C24-oxidation product of 25-hydroxy vitamin D3 and related intermediates in serum of mice treated with 24,25-dihydroxyvitamin D3. *Journal of Steroid Biochemistry* 2013 **136** 54–58. (https://doi.org/10.1016/j.jsbmb.2012.09.012)

77 Wang Z, Schuetz EG, Xu Y & Thummler KE. Interplay between vitamin D and the drug metabolizing enzyme CYP3A4. *Journal of Steroid Biochemistry and Molecular Biology* 2013 **136** 23–28. (https://doi.org/10.1016/j.jsbmb.2012.12.001)

80 Haussler MR & Norman AW. Chromosomal receptor for a vitamin D metabolite. *PNAS* 1969 **62** 155–162. (https://doi.org/10.1073/pnas.62.1.155)

81 Cheng JB, Motola DL, Mangelsdorf DJ & Russell DW. Deorphanization of cytochrome P450 2R1: a microsomal vitamin D 25-hydroxolase. *Journal of Biological Chemistry* 2003 **278** 38084–38093. (https://doi.org/10.1074/jbc.M307028200)

82 Fraser D, Kooh SW, Kind HF, Holick MF, Tanaka Y & DeLuca HE. Pathogenesis of hereditary vitamin-D-dependent rickets. An inborn error of vitamin D metabolism. *PNAS* 2001 **98** 7498–7503. (https://doi.org/10.1073/pnas.13029498)

83 Kato S. Vitamin D 1alphahydroxylase knockout mice as a hereditary rickets animal model. *Endocrinology* 2001 **142** 2734–2735. (https://doi.org/10.1210/endo.142.7.83349)

84 Panda DK, Miao D, Tremblay ML, Sirois J, Farooqui R, Hendy GN & Goltzman D. Targeted ablation of the 25-hydroxyvitamin D 1alpha-hydroxylase enzyme: evidence for skeletal, reproductive, and immune dysfunction. *PNAS* 2001 **98** 7498–7503. (https://doi.org/10.1073/pnas.13029498)

85 St-Arnaud R, Arabian A, Travers R, Barletta F, Raval-Pandya M, Chapin K, Depovere J, Mathieu C, Christakos S, Demay MB, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcaemia. *New England Journal of Medicine* 2001 **345** 410–421. (https://doi.org/10.1056/NEJMoa1003864)

86 Schlingmann KP, Kaufmann M, Weber S, Irwin A, Goos C, Kuwertz-Broking E, Fehrenbach H, et al. Deficient mineralization of intramembranous bone in vitamin D-24-hydroxylase-ablated mice is due to elevated 1,25-dihydroxyvitamin D and not to the absence of 24,25-dihydroxyvitamin D. *Endocrinology* 2000 **141** 2658–2666. (https://doi.org/10.1210/endo.141.7.75759)

87 Deluca HF & Avioli LV. Treatment of renal osteodystrophy with 25-hydroxycholecalciferol. *Archives of Internal Medicine* 1970 **126** 896–899.

88 Brickman AS, Coburn JW, Massey SG & Norman AW. 1,25-Dihydroxyvitamin D3 in normal man and patients with renal failure. *Annals of Internal Medicine* 1981 **40** 161–168. (https://doi.org/10.7326/0003-4819-103.8.1038)

89 Yoshizawa T, Handa Y, Uematsu Y, Takeda S, Sekine K, Yoshihara Y, Kawakami T, Arioka K, Sato H, Uchiyama Y, et al. Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. *Nature Genetics* 1997 **16** 391–396. (https://doi.org/10.1038/ng0897-391)

90 Li YC, Pirro AE & Demay MB. Analysis of vitamin D-dependent calcium-binding protein messenger ribonucleic acid expression in mice lacking the vitamin D receptor. *Endocrinology* 1996 **139** 847–851. (https://doi.org/10.1210/endo.139.3.8803)

91 Lightwood R & Stapleton T. Idiopathic hypercalcaemia in infants. *Lancet* 1953 **265** 255–256. (https://doi.org/10.1126/science.186.4168.1038)

92 Blunt JW & DeLuca HF. A biologically active metabolite of vitamin D. *Science* 1973 **183** 278–282. (https://doi.org/10.1126/science.180.4082.190)

93 Misselwitz J, Klaus G, Kuwertz-Bröking E, Fehrenbach H, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcaemia. *New England Journal of Medicine* 2011 **365** 410–421. (https://doi.org/10.1056/NEJMoa1103864)

94 DeLuca HF. Vitamin D and the drug metabolizing enzyme CYP3A4. [https://doi.org/10.1038/ng0897-391](https://doi.org/10.1038/ng0897-391)

95 Rutherford WE, Bordier P, Marie P, Bruska K, Carter H, Greenwald A, Blondin J, Haddad J, Bricker N & Slapolsky E. Phosphate control and 25-hydroxycalciferol administration in preventing experimental renal osteodystrophy in the dog. *Journal of Clinical Investigation* 1977 **60** 332–341. (https://doi.org/10.1172/JCI108781)

96 Barton DH, Hesse RH, Pechet MM & Bizzarдо E. A convenient synthesis of 1-hydroxyvitamin D3. *Journal of the American Chemical Society* 1973 **95** 2748–2749. (https://doi.org/10.1021/ja00789a090)

97 Holick MF, Semmiler EJ, Snowe HK & DeLuca HF. 1α-Hydroxy derivative of vitamin D3: a highly potent analog of 1a,25-dihydroxyvitamin D3. *Science* 1974 **180** 190–191. (https://doi.org/10.1126/science.180.4082.190)

98 St-Arnaud R, Dardenne O, Prud’homme J, Hacking SA & Goltzman D. Deficient mineralization of intramembranous bone in vitamin D-24-hydroxylase-ablated mice is due to elevated 1,25-dihydroxyvitamin D and not to the absence of 24,25-dihydroxyvitamin D. *Endocrinology* 2000 **141** 2658–2666. (https://doi.org/10.1210/endo.141.7.75759)

99 Barton DH, Hesse RH, Pechet MM & Bizzardo E. A convenient synthesis of 1-hydroxyvitamin D3. *Journal of the American Chemical Society* 1973 **95** 2748–2749. (https://doi.org/10.1021/ja00789a090)

100 Lam HY, Schnoes HK & DeLuca HF. 1α-Hydroxycalciferol in preventing experimental renal osteodystrophy in the dog. *Journal of Clinical Investigation* 1977 **60** 332–341. (https://doi.org/10.1172/JCI108781)

101 Takahashi F, Finch JL, Denda M, Dusso AS, Brown AJ & Slapolsky E. A new analog of 1,25-(OH)2D3, 19-nor-1,25-(OH)2D3, suppresses serum PTH and parathyroid gland growth in uremic rats without elevation of intestinal vitamin D receptor content. *American Journal of Kidney Diseases* 1997 **30** 105–112. (https://doi.org/10.1016/S0272-6386(97)00571-0)

102 Calverley MJ. Synthesis of MC-903, a biologically active vitamin D metabolite analog. *Tetrahedron* 1987 **43** 4609–4619. (https://doi.org/10.1016/S0040-4020(01)86903-9)

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