Vitamin D, disease and therapeutic opportunities

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Abstract | The discovery of the vitamin D endocrine system and a receptor for the hormonal form, 1α,25-dihydroxyvitamin D_3, has brought a new understanding of the relationship between vitamin D and metabolic bone diseases, and has also established the functions of vitamin D beyond the skeleton. This has ushered in many investigations into the possible roles of vitamin D in autoimmune diseases, cardiovascular disorders, infectious diseases, cancers and granuloma-forming diseases. This article presents an evaluation of the possible roles of vitamin D in these diseases. The potential of vitamin D-based therapies in treating diseases for which the evidence is most compelling is also discussed.

Interest in vitamin D has increased enormously during the past decade — another upturn in a long history that began with the discovery of the antirachitic factor and its preparation by ultraviolet irradiation in the 1920s. In the following decade, rickets receded as a major medical problem in the developed world[1], but research into vitamin D then diminished and reached a low point in the mid-twentieth century when vitamin D supplementation was considered to be the cause of idiopathic hypercalcaemia[2]. However, the discovery of the vitamin D endocrine system in 1970 re-awakened interest in the relationship between vitamin D and metabolic bone disease[3].

The discovery that the vitamin D hormone works through a nuclear receptor, and that this receptor is found in tissues not related to calcium and bone, has led to the investigation of vitamin D and its action in a number of other medical areas[3]. High intake of vitamin D in supplemental form is being suggested by a large number of clinical investigators who are interpreting epidemiological measurements as evidence that vitamin D may play a role in the suppression of a large number of diseases. This Review evaluates these concepts and surveys the evidence supporting them. Although there is no doubt that vitamin D provides many health benefits, there is concern that its value in health may be overestimated and its true value diminished in response to over-reaching claims.

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The vitamin D system

There have been many reviews of the vitamin D endocrine system[4,5] and the mechanisms of action of the vitamin D hormone 1α,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$)[6,7], which will not be repeated here. However, a general overview of the system is presented to provide the key background for discussion later of the role of vitamin D in disease.

The main source of vitamin D in humans is the photoconversion of 7-dehydrocholesterol in the epidermis to pre-vitamin D_3, which isomerizes to form vitamin D_3 (REF. 8) (FIG. 1). Vitamin D_3 is then transported to the liver, where it undergoes its first modification by 25-hydroxylase (possibly encoded by *CYP2R1*) to produce the circulating form of vitamin D: 25-hydroxyvitamin D_3 (25-OH-D_3)[9]. At physiological concentrations, 25-OH-D_3 does not seem to have a function of its own, but, rather, is the precursor of the active hormone, 1,25-$(OH)_2D_3$, which is formed predominantly in the kidney and specifically in proximal convoluted tubule cells[10]. The enzyme responsible for this conversion is 25-OH-D-1α-hydroxylase (encoded by *CYP27B1*), which, in the kidney, is tightly regulated by the need for calcium and phosphorus[11].

The primary signal for activating *CYP27B1* transcription in the kidney is parathyroid hormone (PTH). In response to low serum calcium, the parathyroid gland secretes PTH, which (among its many functions) stimulates the transcription of *CYP27B1*, resulting in the production of 1,25-$(OH)_2D_3$ (FIG. 2). Very low blood phosphate also increases *CYP27B1* expression[4]. In turn, 1,25-$(OH)_2D_3$ directly stimulates intestinal calcium and phosphate absorption and, together with PTH, stimulates the synthesis and secretion of a cytokine known as receptor activator of nuclear factor-κB ligand (RANKL), which has a key role in osteoclastogenesis and the activation of giant osteoclasts to induce bone resorption[12,13]. Additionally, 1,25-$(OH)_2D_3$ and PTH are required in

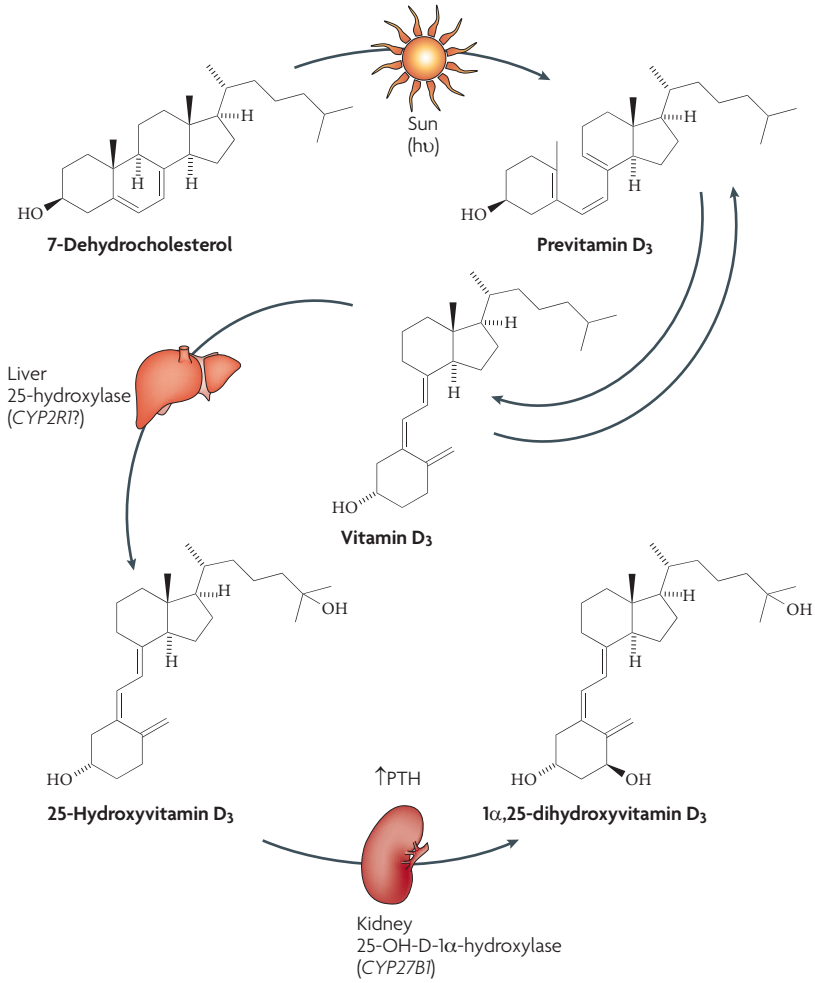


Figure 1 | **Pathway of native hormone or 1α,25-dihydroxyvitamin D_3 production.** The major source of vitamin D_3 is through ultraviolet irradiation of 7-dehydrocholesterol in skin. The liver 25-hydroxylase enzyme (possibly encoded by *CYP2R1*) then converts vitamin D_3 to 25-hydroxyvitamin D_3 (25-OH-D_3), the major circulating form of the vitamin. Generation of 1α,25-dihydroxyvitamin D_3 occurs primarily in the kidney by the 25-OH-D-1α-hydroxylase enzyme (encoded by *CYP27B1*), which is tightly regulated by blood calcium and phosphorus levels, and transcription of this enzyme is directly altered by parathyroid hormone (PTH).

the distal renal tubule to increase calcium reabsorption. Fibroblast growth factor 23 (FGF23) is also a regulator of *CYP27B1* expression and of *CYP24A1* expression (which encodes vitamin D_3 24-hydroxylase, the enzyme that successively modifies 1,25-$(OH)_2D_3$ for excretion)[14]. 1,25-$(OH)_2D_3$ causes secretion of FGF23 in the bone[15], and FGF23 stimulates phosphate excretion while inhibiting 25-OH-D-1α-hydroxylase or *CYP27B1* expression. However, more detail on this regulation is needed at the physiological level. The resultant elevation of serum calcium in turn suppresses the production of PTH, thereby completing the endocrine loop.

The vitamin D hormone 1,25-$(OH)_2D_3$ acts through the vitamin D receptor (VDR), a member of the nuclear receptor superfamily[7]. Ligand-bound VDR requires the retinoid-X receptor as a partner for binding to vitamin D-responsive elements found predominantly, although not exclusively, in the promoter of target genes. Through a complex set of transcription factors, co-activators and co-repressors, transacetylase systems are activated to loosen chromatin, followed by the binding of transcription factors that, together with co-activators, produce an increase in the transcription of target genes or, with co-repressors, can suppress transcription of a gene. Of great importance physiologically is that, through binding to VDR, 1,25-$(OH)_2D_3$ induces expression of *CYP24A1*, which encodes vitamin D_3 24-hydroxylase, the enzyme that successively modifies 1,25-$(OH)_2D_3$, ultimately producing calcitroic acid, a biliary excretion product[16,17]. Vitamin D_3 24-hydroxylase is responsible for the degradation of 1,25-$(OH)_2D_3$ and 25-OH-D_3 and therefore serves as another mechanism for controlling the level of 1,25-$(OH)_2D_3$.

There have also been many reports of non-genomic actions of vitamin D[18]. These have been reported primarily at the cellular level and have not been verified *in vivo*. The concentrations required for these actions are generally very high and unlikely to be of physiological significance.

Following the discovery of the VDR in the mid-1970s[19,20] and its cloning in 1988 (REFS 21,22), its presence in a number of tissues not previously associated with calcium and phosphorus metabolism was discovered, both by immunochemical measurements and by the accumulation of tritiated 1,25-$(OH)_2D_3$ in target nuclei. This discovery triggered an explosion of research directed towards finding functions of vitamin D outside calcium and phosphate homeostasis. The sites at which VDRs are present include the parathyroid gland, pancreatic islet cells, macrophages, promyelocytes, skin keratinocytes, certain specific neural cells, mammary glands, specific cells in the reproductive organs, proximal and distal tubular epithelial cells of the kidney, osteoblasts, and osteoblast and osteoclast precursors[13]. The presence of VDRs in some of these locations and their relation to disease are discussed below.

There has also been much debate and investigation into the possibility of paracrine and/or autocrine functions of the vitamin D system. The majority of the evidence is based on *in vitro* studies and on studies of pathological conditions[13], and *in vivo* evidence supporting autocrine/paracrine functions in normal circumstances is needed before this role can be fully accepted. In disease situations, such as granuloma-forming disease, and in some forms of cancer, there are solid data to support extrarenal synthesis of 1,25-$(OH)_2D_3$, which is also discussed below.

Metabolic bone disease

As discussed above, the primary function of vitamin D is to elevate plasma calcium and phosphorus to normal and supersaturating levels that lead to the mineralization of the skeleton. Administration of vitamin D results in the curing of rickets in children and osteomalacia in adults. Nevertheless, vitamin D-resistant failures in mineralization have been reported (TABLE 1). One such disorder is vitamin D-dependency rickets type I, which has been attributed to defects in *CYP27B1*, which encodes the enzyme responsible for converting the circulating

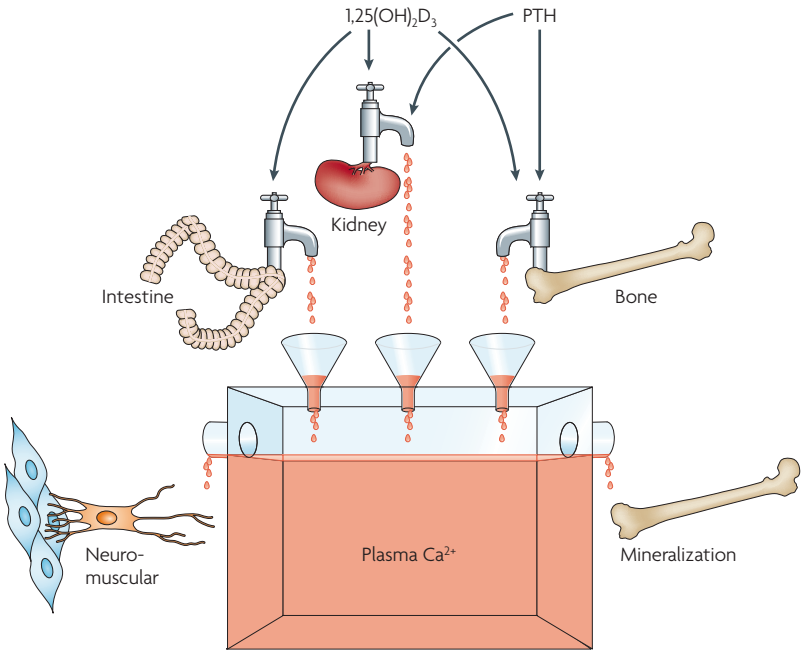


Figure 2 | **Depiction of 1α,25-dihydroxyvitamin D_3 activities and target organs involved in maintaining plasma calcium homeostasis.** 1α,25-dihydroxyvitamin D_3 ($1,25\text{-}(OH)_2D_3$) works in conjunction with parathyroid hormone (PTH) to release calcium from bone stores and reabsorb calcium in the kidney. The vitamin D hormone works alone in promoting active calcium absorption in the intestine. Without proper maintenance of the blood calcium levels, bone is under-mineralized, and, if the calcium levels drop further, neuromuscular function fails and death occurs as a result of tetany.

form of vitamin D to the active hormone. Vitamin D-dependency rickets type I is readily treated by $1,25\text{-}(OH)_2D_3$ itself.

Also of great importance is vitamin D-dependency rickets type II, which results from mutations in the *VDR* gene. Some mutations render the VDR inactive and others modify the VDR so that larger doses of the vitamin D hormone are needed to be effective[23,24]. Thus, treatment of vitamin D-dependency rickets type II with $1,25\text{-}(OH)_2D_3$ has highly variable results, with some patients responding to large doses, whereas others do not[23,24]. Some require the intravenous infusion of calcium and phosphorus[24] to promote mineralization, but there are many defects that these patients suffer from in addition to rickets, including alopecia, hyperparathyroidism, tooth loss, bone pain, cardiac hypertrophy and/or hearing loss[25]. Animal models of both type I and type II rickets have been produced. In particular, *Vdr*-knockout mice, first generated in the laboratories of Kato and Demay, and the *Cyp27b1*-knockout animals produced in the laboratories of St Arnaud, Goltzman and DeLuca[26,27], have been very useful tools in elucidating the functions of vitamin D.

The involvement of vitamin D in osteoporosis is still under investigation. A double deficiency of calcium and vitamin D produces an osteoporotic condition[28]. However, osteoporosis in postmenopausal women and in ageing males is a multifactorial disease. Vitamin D insufficiency is often encountered in such patients and probably contributes to the disease process; however, vitamin D_3 or vitamin D_2, even at high doses, does not provide a significant therapeutic effect in these patients. In general, age-related changes include increased PTH levels and lower VDR amounts in the intestine and bones[29,30], which suggest a particular need for $1,25\text{-}(OH)_2D_3$ to redress the balance. The loss of oestrogen also reduces $1,25\text{-}(OH)_2D_3$ synthesis and results in lower VDR levels in bones and intestine[31–33]. More recently, there has been evidence showing that $1,25\text{-}(OH)_2D_3$ has some anabolic bone activity, as demonstrated in the *Pth*- and *Cyp27b1*-knockout mouse models[34].

Analogues of vitamin D that have anabolic properties have been prepared[35–37]. One such analogue is 2MD (2-methylene-19-nor-(20*S*)-$1\alpha,25\text{-}(OH)_2D_3$) (FIG. 3), which is at least 100 times more potent than $1,25\text{-}(OH)_2D_3$ in stimulating both osteoclast and osteoblast activity, resulting in profound increases in bone mass in rats[35–37]. However, because both bone resorption as well as formation are stimulated, 2MD does not increase bone mass in postmenopausal women[38].

There is no doubt that adequate vitamin D intake is important in patients suffering from osteoporosis, and in some countries where there is low calcium intake, beneficial effects of $1,25\text{-}(OH)_2D_3$ or its prohormone in treating osteoporosis have been clearly demonstrated[39]. Furthermore, vitamin D_3 is often included with bisphosphonates or with calcium in the treatment of osteoporosis. Their activity in increasing bone mass is modest, but they do seem to reduce the fracture rate[40,41]. The use of vitamin D analogues for the treatment of osteoporosis is still being explored, with the recent development of ED-71 (2-(3-hydroxypropoxy)calcitriol) by Chugai Pharmaceuticals (FIG. 3), which seems to be an improvement on $1,25\text{-}(OH)_2D_3$ as a treatment for this disease[39]. Typically, 1–2% increases in bone mineral density are observed after 1 year of $1,25\text{-}(OH)_2D_3$ administration, whereas a 3% increase was observed with ED-71 after 1 year[42].

A type of rickets that results from a severe lack of calcium has been reported in Africa, but is rare elsewhere[43]. Another disease called hypophosphataemic rickets is not a vitamin D-related disorder[44]. Vitamin D therapies have been used in X-linked hypophosphataemic rickets with varying success, often with the complication of hypercalcaemia and unwanted calcification of organs[45]. Hypophosphataemic rickets is best treated by aggressive provision of phosphate together with adequate amounts of the active form of vitamin D to promote assimilation of phosphate supplements[45].

Overall, the use of vitamin D in metabolic bone disease is a genuine success story and is clearly an area in which these compounds are required for prevention of disease on the one hand and present possible therapies on the other. Development of vitamin D analogues that possess anabolic activity and can be delivered orally would fulfil an unmet need in osteoporosis therapy.

Kidney disease

There is clear evidence showing that chronic renal failure — for example, resulting from polycystic kidney disease or diabetic nephropathy — is associated with severe

Table 1 | **Metabolic bone diseases**

	Rickets (children), osteomalacia (adults)	Osteopaenia, osteoporosis
Disorder	Decreased mineralization	Decreased bone mass with (osteoporosis) or without (osteopaenia) fracture
Causes	Nutrition, kidney failure, genetics	Nutrition, menopause, genetics
Treatment	• Type I: (25-OH-D-1α-hydroxylase defect) 1α,25-dihydroxyvitamin D_3 or high doses of vitamin D • Type II: (VDR defect) calcium, phosphate or high doses of 1α,25-dihydroxyvitamin D_3 • X-linked hypophosphataemia: phosphate ± 1α,25-dihydroxyvitamin D_3	• Bisphosphonates • SERMs • Antibody to RANKL • Calcitonin • Parathyroid hormone • Oestrogen • Vitamin D hormone analogues

RANKL, receptor activator of nuclear factor-κB ligand; SERMs, selective oestrogen receptor modulators; VDR, vitamin D receptor.

metabolic bone disease[46]. A discussion of how metabolic bone disease results from renal failure is beyond the scope of this Review; however, the loss of renal function carries with it the loss of function of the vitamin D endocrine system and in this respect is a serious disorder of vitamin D metabolism.

As the ratio of PTH to 1,25-$(OH)_2D_3$ level in the plasma rises, there is a sequence of events leading to renal osteodystrophy accompanied by secondary hyperparathyroidism[47]. Following its original discovery in 1970, 1,25-$(OH)_2D_3$ and its synthetic precursor, 1α-hydroxyvitamin D_3 (alfacalcidol) received immediate attention as a possible therapy for renal osteodystrophy, given that the kidney is the organ that synthesizes 1,25-$(OH)_2D_3$. Later, however, it was discovered that the VDR is found in the parathyroid glands[48,49] and that a major function of vitamin D is to suppress parathyroid cell proliferation and the expression of the preproparathyroid gene[50].

This has led to the development of a series of vitamin D analogues that are useful in managing the secondary hyperparathyroidism associated with chronic renal failure[51]. Presumably, this also improves the bone status of these patients. Currently, 19-nor-1,25-dihydroxyvitamin D_2 (paricalcitol), 1α-hydroxyvitamin D_2 (doxercalciferol), alfacalcidol, 1,25-$(OH)_2D_3$ (calcitriol) and 22-oxa-1,25-dihydroxyvitamin D_3 (oxacalcitriol) are used for the treatment of secondary hyperparathyroidism (TABLE 2). All of these 1,25-$(OH)_2D_3$ analogues have achieved market success, as they offer a wider therapeutic window compared with 1,25-$(OH)_2D_3$ and 1α-hydroxyvitamin D_3. However, the basis for the improvement is different for each compound. Paricalcitol seems to have more tissue-specific activity than 1,25-$(OH)_2D_3$ (REF. 52). Doxercalciferol bypasses first-pass metabolism and also contains a D_2 side chain, which lowers the calcaemic liability[53]. The lower toxicity of oxacalcitriol is thought to be due to its short half-life in the circulation[54].

Recently, the finding that 1,25-$(OH)_2D_3$ suppresses renin levels[55] has led to the exploration of these analogues for their potential use as a therapy in early stages of kidney disease. Because of the known properties of renin (FIG. 4), coupled with the knowledge that the leading cause of death for kidney disease patients is cardiovascular failure, this molecular target of vitamin D action serves as a potential link between therapy with 1,25-$(OH)_2D_3$ or its analogues and increased survival of patients with chronic renal failure[56]. Furthermore, recent evidence suggests that therapy with 1,25-$(OH)_2D_3$ or its analogues at earlier stages of kidney disease in conjunction with an angiotensin-converting enzyme or angiotensin-II-receptor blocker might delay the progress of the disease[57–59].

Heart disease

Importantly, there is a high incidence of vascular disease and cardiovascular death in patients with renal failure, in whom there is a failure of the production of the vitamin D hormone[60]. Epidemiological studies have shown that treatment with vitamin D compounds (1,25-$(OH)_2D_3$, alfacalcidol and paricalcitol) increases the life expectancy of patients with renal failure[56], suggesting that vitamin D might have an important role in cardiovascular disease, because this is the primary cause of death in this group of patients.

Whether heart muscle is a target of vitamin D remains controversial, as the VDR has been identified in this tissue by some researchers and not by others[177]. However, left-ventricular hypertrophy is found in 25-OH-D-1α-hydroxylase-deficient mice and in 5/6-nephrectomized rats[61,62]. Left-ventricular hypertrophy is also found in dialysis patients. Importantly, recent epidemiological studies showed a relationship between blood levels of 25-OH-D_3 and the incidence of stroke[63,64]; however, it should be noted that these are correlations and not cause-and-effect studies. Heart lesions found in 25-OH-D-1α-hydroxylase-deficient mice[62] certainly indicate a role of vitamin D, either indirect or direct, in cardiovascular health.

As reviewed recently[65], there have been several randomized clinical trials measuring the effect of vitamin D supplementation on blood pressure; however, to date, the results do not conclusively solidify the importance of vitamin D in cardiovascular health. Nevertheless, the results are sufficient to indicate a relationship, and additional clinical studies will reveal the true basis for a role of vitamin D in cardiovascular health.

Skin disorders

Psoriasis. Skin is a target of vitamin D action, as has been clearly established by the presence of the VDR in keratinocytes, sebocytes and dermal papilla cells[48,66–68], and by the suppression of keratinocyte proliferation *in vitro* by 1,25-$(OH)_2D_3$ (REF. 69). The discovery that 1,25-$(OH)_2D_3$ suppresses keratinocyte proliferation and causes differentiation of promyelocytes to monocytes stimulated interest in the effects of 1,25-$(OH)_2D_3$ on keratinocytes[70]. Topical application of 1,25-$(OH)_2D_3$ showed promise as a treatment in psoriasis, which is characterized by the hyperproliferation of keratinocytes[71]. However, concerns regarding hypercalcaemia drove the search for analogues with a wider therapeutic index, and Leo Pharmaceuticals

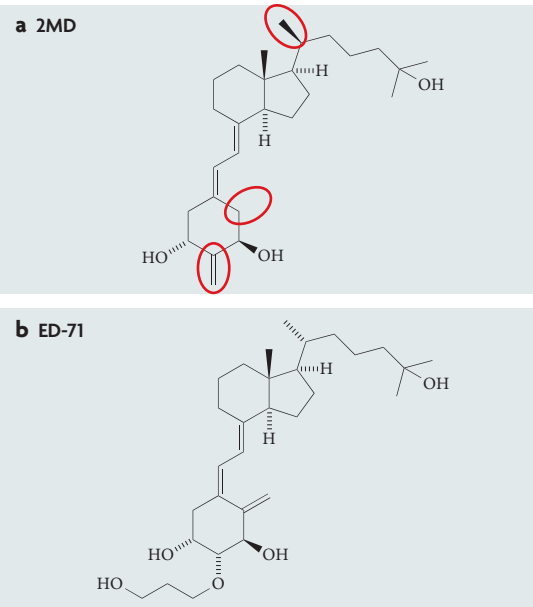


Figure 3 | **Vitamin D analogues for osteoporosis.** **a** | 2MD (2-methylene-19-nor-(20S)-1α,25-$(OH)_2D_3$) is an analogue developed in DeLuca's laboratory and is under development by Deltanoid Pharmaceuticals as an oral therapy. It is at least 100 times more potent than 1α,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) in stimulating both osteoclast and osteoblast activity, resulting in profound increases in bone mass[33,34,35]. 2MD and the natural hormone are equipotent in stimulating intestinal calcium transport, therefore indicating a wider therapeutic window for 2MD. Other analogues containing the same A-ring with modified side chains have similar profiles to 2MD (unpublished observations). The three red ovals depict the structural differences from 1,25-$(OH)_2D_3$. **b** | ED-71 (2-(3-hydroxypropoxy)calcitriol) is also a vitamin D analogue that is in development for oral treatment of osteoporosis by Chugai Pharmaceuticals. This compound has a longer lifetime in the body due to its higher affinity for vitamin D-binding protein.

developed the analogue MC-903 (calcipotriol), which is sold under the trade name of Dovonex for the topical treatment of plaque psoriasis[72]. More recently, 22-oxa-1,25-$(OH)_2D_3$ (oxacalcitriol) was developed by Chugai Pharmaceuticals as a therapy for plaque psoriasis[73] (TABLE 2). Vitamin D analogues are highly effective therapeutics in this disorder, and it is likely that improved analogues for this indication will appear. New analogues that require less frequent application or are effective in an oral dosage form would be highly desirable for treatment of this disease.

Acne. A promising new application for vitamin D-based therapeutics is in acne, which has traditionally been treated by 13-*cis*- and all-*trans*-retinoic acid. There are many other treatments for acne besides the retinoid compounds, but the retinoids are widely used even though they have many side effects, including disturbances in reproduction and sensitivity of skin to light, in addition to skin irritations[74]. Recent work has revealed that some shortened side-chain, but not full side-chain, analogues of the vitamin D hormone can be effective in the Rhino mouse model of acne[75], indicating the potential use of such compounds for the treatment of this disorder. An understanding of the structural selectivity of these analogues awaits further studies.

Autoimmune diseases

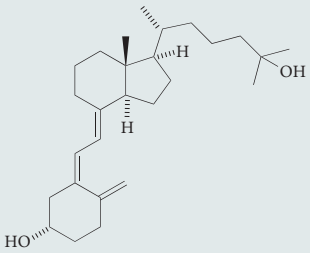
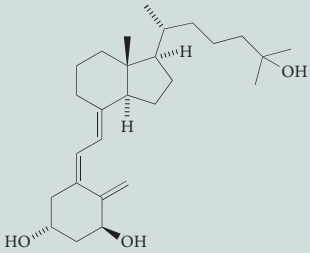
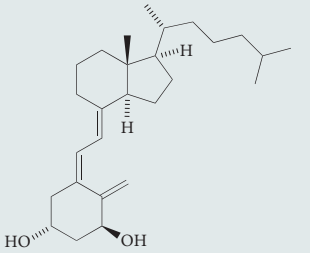
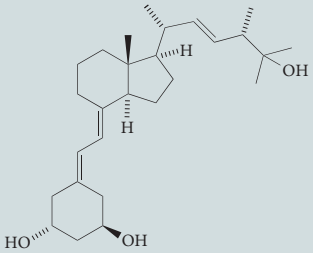
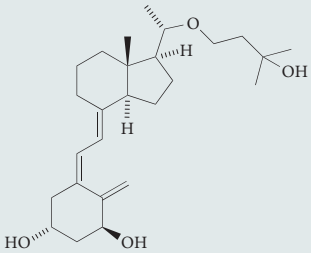
The possibility that vitamin D may have a role in autoimmune diseases is based on the discovery of the VDR in immune-system cells such as antigen-presenting cells, macrophages and activated T cells[76–78]. Many *in vitro* experiments demonstrating the effects of the vitamin D compounds on stimulating or inhibiting the proliferation of T helper 1 (T_H1) and T_H2 cells have been published[79], but the interpretation of these in terms of autoimmune disease is difficult. Nevertheless, the discovery in 1993 that T cell-mediated inflammation could be suppressed by vitamin D compounds, particularly by 1,25-$(OH)_2D_3$, sparked interest in the possible use of vitamin D in treating autoimmune disease[80].

For example, as early as 1974, an inverse relationship between exposure to ultraviolet light and the incidence of multiple sclerosis had been noted[81]. The incidence of multiple sclerosis cases was observed to be low in countries near the equator and to increase progressively in countries closer to the poles. An extrapolation was made that this might be due to vitamin D, and similar links have been made for other immune disorders, as described further below.

Multiple sclerosis. Treatment with 1,25-$(OH)_2D_3$ can suppress the symptoms in experimental autoimmune encephalomyelitis (EAE) in mice (a model of multiple sclerosis)[82–84]. However, treatment of EAE with 1,25-$(OH)_2D_3$ requires calcium in the diet in amounts that result in hypercalcaemia[85,86]. As equatorial countries have a low incidence of multiple sclerosis without hypercalcaemia, clearly some other factor must be involved. A recent study has suggested that ultraviolet light may have an ameliorating effect on this disorder, independent of vitamin D[87]. Whether multiple sclerosis can be suppressed by either vitamin D or 1,25-$(OH)_2D_3$ has yet to be definitively investigated in large studies. Two very small clinical studies have been reported, whereby 19-nor-1,25-dihydroxyvitamin D_2 or 1,25-$(OH)_2D_3$, although increasing urinary or serum calcium, had no consistent impact on the symptoms of multiple sclerosis[88,89]. Therefore, it seems probable that vitamin D is only one part of the story of the effect of sunlight on multiple sclerosis.

Type 1 diabetes. Another autoimmune disease in which vitamin D has a role is type 1 diabetes. Treatment with 1,25-$(OH)_2D_3$ reduced the symptoms of type 1 diabetes in the non-obese diabetic (NOD) mouse[90]. Vitamin D deficiency in NOD mice increased the incidence and severity of this disease[91]. Furthermore, epidemiological studies have shown a relationship between sunlight exposure and the incidence of type 1 diabetes[92]. Again, this is only a correlation and may involve an immune

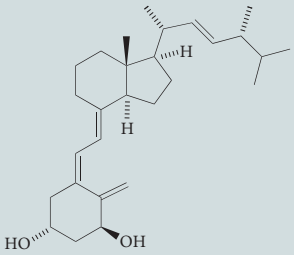
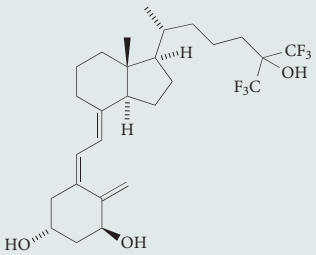
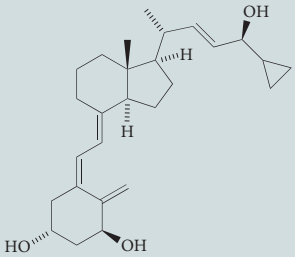
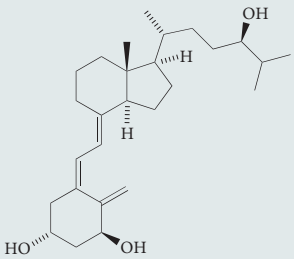
Table 2 | **Marketed or previously marketed vitamin D therapies**

Compound	Chemical structure	Trade name	Company	Disease indication
25-hydroxy-vitamin D_3 (calcidiol)		Calderol	Upjohn	Renal osteodystrophy
			Organon	Osteoporosis
		Didrogyl, Dedrogyl	Roussel and others	Rickets, spasmophilia and others
		Hidroferol	Faes Farma	Renal osteodystrophy, rickets and others
1α,25-dihydroxy-vitamin D_3 (calcitriol)		Rocaltrol	Roche	Renal osteodystrophy
				Osteoporosis
		Calcijex	Abbott	Renal osteodystrophy
		Silkis, Vectical	Galderma	Psoriasis
1α-hydroxy-vitamin D_3 (alfacalcidol)		Alfarol	Chugai	Osteoporosis
		Alfarol	Chugai	Renal osteodystrophy, secondary hyperparathyroidism, rickets
		One-Alpha, EinsAlpha, Etalpha	Leo Pharma	Renal osteodystrophy
		Alpha D_3	Teva Pharmaceuticals	Osteoporosis
1,25-$(OH)_2$-19-nor-dihydroxy-vitamin D_2 (paricalcitol)		Zemplar	Abbott	Secondary hyperparathyroidism
22-oxa-1,25-dihydroxyvitamin D_3 (oxacalcitriol)		Oxarol injection	Chugai	Secondary hyperparathyroidism
		Oxarol ointment	Chugai	Psoriasis

response that is independent of vitamin D. As yet, a clear demonstration that vitamin D compounds reduce the incidence of type 1 diabetes in humans awaits a randomized controlled trial in other parts of the world that are less prone to vitamin D deficiency. Two observational studies conducted in northern Europe indicated a reduced incidence of type 1 diabetes in infants given vitamin D supplements[93].

Inflammatory bowel disease (IBD). IBD, which comprises Crohn's disease and ulcerative colitis, is another autoimmune disease for which experimental work has suggested that vitamin D compounds may be useful in reducing the symptoms of this disorder[94,95]. Again, this is an inflammatory reaction involving T cells, but it is unclear whether IBD can be successfully treated with a vitamin D compound without causing hypercalcaemia[96].

Table 2 (cont.) | **Marketed or previously marketed vitamin D therapies**

Compound	Chemical structure	Trade name	Company	Disease indication
1α-hydroxy-vitamin D_2 (doxercalciferol)		Hectorol	Bone Care International/ Genzyme	Secondary hyperparathyroidism
1,25-$(OH)_2$-26,27-F_6-vitamin D_3 (falecalcitriol)		Hornel	Taisho Pharmaceuticals/ Sumitomo Pharmaceuticals	Secondary hyperparathyroidism
		Fulstan	Kissei Pharmaceuticals	Secondary hyperparathyroidism
MC-903 (calcipotriol)		Daivonex, Dovonex	Leo Pharmaceuticals/ Warner Chilcott	Psoriasis
1,24-dihydroxy-vitamin D_3 (tacalcitol)		Bonalfa	Teijin	Psoriasis
		Curatoderm	Merck KgaA	Psoriasis

Lupus erythematosus. Lupus is another autoimmune disorder in which numerous symptoms, including lupus nephritis, sclerosis and skin lesions, are present. Current epidemiological and preclinical work suggests that an analogue of vitamin D may be useful in the treatment of lupus, in particular, lupus nephritis[97,98], but again no clinical evidence is available to support these studies.

Rheumatoid arthritis. Rheumatoid arthritis is an autoimmune disease that seems to respond to 1,25-$(OH)_2D_3$ treatment in animal models. So far, however, active forms of vitamin D have not yet been developed for the treatment of this disorder[99]. A small intervention study with 1-OH-D_3 showed positive effects on reducing disease activity in patients suffering from rheumatoid arthritis[100]. Historically, large doses of vitamin D_3 or vitamin D_2 were used as a treatment for this disease, but did not prove to be of value and presented the danger of vitamin D intoxication[101,102].

Summary of vitamin D in autoimmune disease. The question of the potential of using vitamin D compounds to treat autoimmune diseases is one of great importance and has yet to be satisfactorily answered. Although it is clear that vitamin D alone may not completely explain the relationship between autoimmune diseases and sunlight exposure, the evidence that vitamin D hormone deficiency increases disease incidence or symptoms, and that vitamin D compounds can ameliorate symptoms and/or delay disease in mouse models of type 1 diabetes and IBD, suggests that vitamin D does have a role in such diseases[91,103]. Furthermore, the fact that the VDR is found in large amounts in the islet cells of the pancreas and cells of the immune system is another reason to speculate that vitamin D therapeutics may be useful in these disorders[76–78,104]. A number of mechanistic studies have been conducted with regard to vitamin D and how it might suppress autoimmune disorders. However,

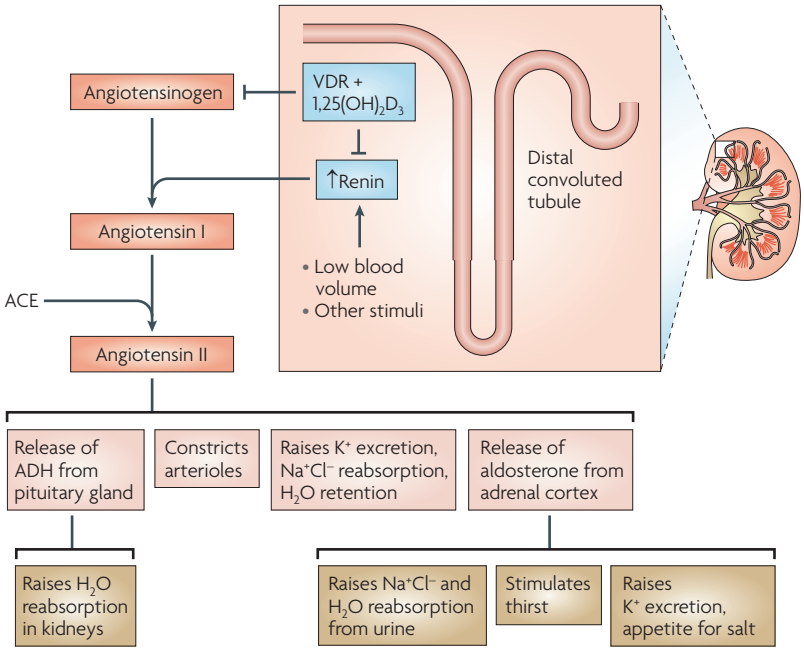


Figure 4 | **The link between the vitamin D and RAAS systems.** The renin–angiotensin–aldosterone system (RAAS) is known to have a vital role in maintaining blood pressure and blood volume. The discovery that 1α,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) can decrease renin (at the mRNA level) and angiotensin (possibly through the nuclear factor κB pathway) levels provides a possible mechanism for positive effects of vitamin D hormone on the cardiovascular system. In addition, this mechanism of action indicates the possibility of synergistic effects of combination therapy, that is, vitamin D hormone or analogues with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker. ADH, antidiuretic hormone; VDR, vitamin D receptor.

until the suppression of these diseases by vitamin D compounds can be accomplished without hypercalcaemia, these findings can be of only academic interest. As will be discussed in the section '*Analogues of vitamin D for the treatment of disease*', there are a number of new analogues that have lower potencies in organs that are responsible for affecting blood calcium levels, but these potencies in autoimmune disease targets remain untested and/or unknown.

Cancer

A role for the vitamin D system in cancer was first suggested by cell culture studies using melanoma and leukaemia cell lines[70,105]. In these *in vitro* studies, 1,25-$(OH)_2D_3$ was shown to inhibit proliferation and cause the differentiation of the cells at concentrations of ~1 nM. Since then, a large number of epidemiological studies have been published showing inverse relationships between cancer incidence and ultraviolet irradiation, vitamin D intake and/or circulating levels of 25-OH-D_3 (REFS 106–108). Other correlations between cancer and vitamin D include the season of diagnosis, obesity and skin colour: lower survival rates occur when diagnosis is made in winter or spring, and obese and dark-skinned individuals have lower 25-OH-D_3 levels and higher cancer mortality rates[109–111].

A number of preclinical *in vivo* studies have been conducted to assess the utility of some form of vitamin D for the prevention or treatment of various cancers[112,113]. Mixed outcomes were seen, with some of the results supporting the epidemiological findings, whereas others did not. One of the more informative studies showed that the *Vdr*-knockout mouse had greater susceptibility to 7,12-dimethylbenz[α]anthracene (DMBA)-induced cancers of the skin, lymph nodes and thymus, but not mammary gland, ovary, uterus, lung or liver[114]. Although a variety of cellular mechanisms, such as modulation of cell cycle arrest, apoptosis and differentiation, and inhibition of angiogenesis, have been proposed to explain the anticancer activities of vitamin D, support for such actions in either animals or humans is not convincing[24,115].

Very few large-scale cancer intervention trials using vitamin D compounds for prevention or treatment have been completed in humans. Furthermore, the outcomes of the limited clinical trials shown in TABLE 3 have not been consistent. The largest number of clinical trials using a form of vitamin D therapy have been for patients with prostate cancer. The therapy that showed the most promise was one in which 1,25-$(OH)_2D_3$ was given at a high dose (45 μg) once a week in combination with docetaxel (TABLE 3). However, the Phase III trial was terminated early, because the survival rate in the treated group was lower than in the placebo group[116]. For colorectal cancer, an intervention trial involving 36,282 patients given vitamin D showed no reduction in cancer risk, whereas a small trial using nearly three times more vitamin D supplementation did show a protective effect[117,118] (TABLE 3). The only large intervention trial reported to date for breast cancer does not support the use of vitamin D for prevention of this form of cancer[119]. In addition two smaller studies using vitamin D hormone analogues did not provide strong evidence for treatment of advanced breast cancer (TABLE 3).

Other cancers, such as pancreatic, skin, lymphoma and ovarian, have also been suggested as potential targets for vitamin D therapy[120–123]. However, no clinical trials using vitamin D or a derivative have been reported for skin or ovarian cancer, and a small trial using an analogue of 1,25-$(OH)_2D_3$ for pancreatic cancer treatment did not show any reduction in tumour burden[124]. Two trials conducted in patients with non-Hodgkin's lymphoma and 1α-OH-D_3 as a therapy showed some promise for a vitamin D compound treating this form of cancer[125,126]. Interestingly, the treatment of patients suffering from advanced hepatocellular carcinoma with an analogue of 1,25-$(OH)_2D_3$ resulted in two patients experiencing complete remission, a rare occurrence with this intractable form of cancer[127].

The lack of commercial success so far with vitamin D-related therapy for cancer could be due to several possibilities. Epidemiological studies are simply correlative relationships and cannot be used to determine cause and effect. Furthermore, the blood analyses of 25-OH-D_3 are unreliable in a large number of the reported studies due to assay problems, and the relationship to vitamin D intakes are also questionable given that some vitamin D supplements do not contain the amount stated on the bottle[128,129]. Preclinical animal models all have inherent problems[130] and the results are not universally supportive.

Table 3 | **Summary of clinical trials in cancer using vitamin D, hormone or analogue, as an intervention***

Subjects	Treatment regimen	Results	Refs
Breast cancer			
Patients with advanced breast cancer (*n* = 19)	• 100 μg calcipotriol • Topical; once daily • Duration: 6 weeks	Five patients withdrew before end of treatment; three showed reduction (50%) in diameter of lesions; five had disease progression; and five had no change	159
Patients with advanced breast cancer (*n* = 14)	• 0.15–17 μg per m^2 EB1089 • Oral? once daily • Duration: 10–234 days	Four patients showed stabilization of disease in excess of 3 months; no improvements observed	160
Postmenopausal women (*n* = 36,282 split into two groups)	• 200 IU vitamin D_3 + 500 mg calcium • Oral; twice daily • Duration: 7 years	No difference in breast cancer incidence compared with placebo	119
Colorectal cancer			
Patients with advanced colorectal cancer (*n* = 6)	• 1.2–12.5 μg per m^2 EB1089 • Oral? twice daily • Duration: 13–147 days	Two patients showed stabilization of disease in excess of 3 months; no improvements observed	160
Postmenopausal women (*n* = 36,282 split into two groups)	• 200 IU vitamin D_3 + 500 mg calcium • Oral; twice daily • Duration: 7 years	No difference in colorectal cancer incidence compared with placebo	118
Postmenopausal women (*n* = 1,179 split into three groups)	• 1,100 IU vitamin D_3 + 1,500 mg calcium • Oral; once daily • Duration: 4 years	Lower incidence of colorectal cancer compared with calcium alone	117
Head and neck cancer			
Patients with head and neck squamous cell carcinoma (*n* = 12)	• 20 μg or 40 μg calcidiol • Oral; once daily • Duration: 6 weeks	No reduction in tumour mass	161
Leukaemia			
Patients with acute myeloid leukaemia (*n* = 29)	• Calcitriol + cytarabine, hydroxyurea • Duration: 3+ weeks	45% had complete remission and 34% had partial remission	162
Liver cancer			
Patients with advanced hepatocellular carcinoma (*n* = 33)	• 10 μg EB1089 • Oral; once daily • Duration: 12+ weeks	Two patients had complete responses; 12 patients had disease stabilization	127
Lymphoma			
Patients with low-grade non-Hodgkin's lymphoma (*n* = 10)	• 1 μg alfacalcidol • Oral; once daily • Duration: 3+ weeks	Three patients achieved partial remission; one patient showed complete remission	125
Patients with low-grade non-Hodgkin's lymphoma (*n* = 32)	• 1 μg alfacalcidol • Oral; once daily • Duration: 8+ weeks	Four patients achieved partial remission and four showed complete remission; disease stabilization shown in 10 patients	126
Mixed			
Patients with advanced malignancies (*n* = 42)	• 1.3–45 μg per m^2 ILX23-7553 • Oral; once daily for 5 days every 2 weeks • Duration: 12–243 days (average = 54)	Eight patients had stable disease for 40–243 days	163
Patients with advanced solid tumours (*n* = 30)	• 10–96 μg calcitriol + gefitinib • Intravenous; once weekly (not week 2) • Duration: median = 8 weeks	Three patients had disease stabilization lasting 4–8 months	164
Patients with advanced solid tumours (*n* = 20)	• 57–163 μg calcitriol + gefitinib + dexamethasone • Intravenous; once weekly (not week 2) • Duration: median = 8 weeks	No antitumour activity observed	165

Clinical trials using vitamin D hormone or analogues have been conducted primarily in late stages of the disease and with low levels of vitamin D, and perhaps therapy with vitamin D compounds will only work in early stages of disease or in prevention and/or with large amounts of the drug. In addition, molecular analysis of tumours has revealed some potential hurdles, such as low VDR expression and high levels of 24-hydroxylase[131]. However, there are reports with findings that are in complete contrast to those just listed, suggesting that

Table 3 (cont.) | **Summary of clinical trials in cancer using vitamin D, hormone or analogue, as an intervention***

Subjects	Treatment regimen	Results	Refs
Pancreatic cancer			
Patients with inoperable pancreatic cancer (*n* = 14)	• 10–15 μg EB1089 • Oral; once daily • Duration: 8+ weeks	Five patients had disease stabilization	124
Prostate cancer			
Patients with hormone-refractory prostate cancer (*n* = 13)	• 0.5–1.5 μg calcitriol • Oral; once daily • Duration: 3+ weeks	Two patients had PSA decreases of 25% and 45%; no other responses observed	166
Patients with recurrent prostate cancer (*n* = 7)	• 0.5–2.5 μg calcitriol • Oral; once daily • Duration: 6–15 months	Six out of seven patients had a decreased rate of PSA increase	167
Patients with hormone-refractory prostate cancer (*n* = 25)	• 5-15 μg doxercalciferol • Oral; once daily • Duration: 8+ weeks	Two patients had partial responses and five had disease stabilization for ≥6 months	168
Patients with increasing PSA after prostectomy or radiation for prostate cancer (*n* = 22)	• 0.5 μg per kg calcitriol • Oral; once weekly • Duration: 2–25+ months (median = 10 months)	Three patients had a PSA reduction of 10–47%; three patients had an increase in PSA-doubling time	169
Patients with advanced androgen-independent prostate cancer (*n* = 20)	• 5–12.5 μg doxercalciferol • Oral; once daily • Duration: 8+ weeks	Six patients had disease stabilization for >6 months	170
Patients with metastatic androgen-independent prostate cancer (*n* = 37)	• 0.5 μg per kg calcitriol + docetaxel • Oral; once weekly • Duration: 8–93+ weeks (median = 43 weeks)	30 out of 37 patients had a 50% or greater reduction in PSA levels; partial response was found in 8 of 15 patients with measurable disease	171
Patients with metastatic androgen-independent prostate cancer (*n* = 17)	• 0.5 μg per kg calcitriol + carboplatin • Oral; once weekly • Duration: 3–44+ weeks (median = 13 weeks)	One patient had a 50% reduction in PSA; four patients had 24–38% reductions in PSA	172
Patients with advanced androgen-insensitive prostate cancer (*n* = 18)	• 5-25 μg paricalcitol • Intravenous; three times per week • Duration: unknown	One patient showed a 23% decline in PSA and another patient showed a dose-dependent decrease in PSA; no effect on survival noted	173
Patients with androgen-independent prostate cancer (*n* = 24)	• 60 μg calcitriol + docetaxel + estramustine • Oral; once per 3 weeks • Duration: mean = five cycles or five doses of calcitriol	55% of patients met PSA-response criteria	174
Patients with androgen-independent prostate cancer (*n* = 35)	• 8–12 μg calcitriol + dexamethasone • Oral; three times per week • Duration: 12+ weeks	Eight patients had PSA decreases of ≥50% for at least 28 days	175
Patients with metastatic androgen-independent prostate cancer (*n* = 250 split into two groups)	• 45 μg calcitriol (DN-101) + docetaxel • Oral; once weekly • Duration: median = 18.3 months	No statistically significant PSA response was observed compared with placebo; no tumour response was seen; increased survival was observed	176

*Only trials with some measure of efficacy are included in this table. PSA, prostate-specific antigen.

either the histochemical analyses are flawed and/or there is heterogeneity of tumours[178]. Careful use of antibodies for these types of analyses should enable resolution of these discrepancies[132]. Clinical studies using protocols that include molecular analysis of the tumour cells could assist in understanding responders versus non-responders and whether or not treatment with this class of compounds has any efficacy. Finally, there is a huge discrepancy between the effective doses used in cell culture studies and the attainable circulating levels in the body or the tumour tissue itself, which suggests that targeted delivery to the site of the cancer and/or the use of analogues that are refractory to 24-hydroxylase activity or have selective uptake by the cancerous cells is needed. The role of vitamin D in the prevention of cancer and the use of vitamin D hormone or analogues for cancer therapy still remains an open question.

Infectious disease

There has been a long history documenting the relationship between sunlight, vitamin D and tuberculosis[133]. More recent studies indicate that vitamin D could be beneficial to patients suffering from this disease. Of particular interest is the report that 1,25-$(OH)_2D_3$ induces the synthesis of cathelicidins and other peptides that provide cellular immunity[134]. This finding has yet to be

adequately explored at the clinical level. So far, only one small study has been conducted in which vitamin D deficiency increases the progression of tuberculosis, and there are inconsistent reports of vitamin D reducing the risk of infectious diseases of the upper respiratory tract[135,136].

Hypercalcaemia

Vitamin D excess. Vitamin D taken in excess is toxic and has been responsible for several documented deaths[137]. Toxicity results from elevated serum calcium and phosphate, causing mineralization of the kidneys, heart, aorta, other blood vessels and cutaneous tissue[137]. The symptoms of vitamin D toxicity are headache, nausea, diarrhoea, polyuria, thirst and malaise. Although hypercalcaemia has been reported at intakes of 2,000 IU per day (50 μg calciferol), this report[138] does not verify the strength of the preparation used and has not been supported by subsequent studies. Clear evidence of hypercalcaemia can be shown at doses of above 25,000 IU per day (625 μg per day)[137,139,140]. Importantly, vitamin D toxicity cannot result from ultraviolet irradiation of the skin, because the levels of 7-dehydrocholesterol in skin are limited, or continued irradiation converts previtamin D to inactive products[139,140].

As described earlier, the production of 1,25-$(OH)_2D_3$ in the kidney is tightly regulated. Furthermore, 1,25-$(OH)_2D_3$, through a feedback loop, induces the expression of *CYP24A1*, which ultimately leads to the degradation of 1,25-$(OH)_2D_3$. How then is toxicity occurring if vitamin D is not converted to 1,25-$(OH)_2D_3$? Toxicity occurs when serum 25-OH-D_3 levels rise to 500 ng per ml or above[141]. Under these conditions, 1,25-$(OH)_2D_3$ levels fall to almost undetectable levels. This is understandable because the conversion of vitamin D to 25-OH-D_3 is regulated largely by the available vitamin D. On the other hand, production of 1,25-$(OH)_2D_3$ is suppressed by high serum calcium and phosphate and the absence of PTH. 25-OH-D_3 can, at high concentrations, bind to VDR and become transcriptionally active[142,143], giving rise to excessive bone resorption and intestinal absorption of calcium and phosphate. The fact that 25-OH-D_3 or vitamin D is equally hypercalcaemic in 25-OH-D-1α-hydroxylase-deficient mice clearly establishes that 1,25-$(OH)_2D_3$ is not the toxic agent and that 25-OH-D_3 is the probable toxicant[142]. On the basis of experiments in the rat, if 25-OH-D_3 is kept below 250 ng per ml, toxicity should not occur unless some other disease process is occurring[141].

Granuloma-forming disease. There are many causes of hypercalcaemia, but, with the discovery of the vitamin D activation system, a new understanding has helped to segregate the causes of this disorder. One cause of hypercalcaemia includes extrarenal production of 1,25-$(OH)_2D_3$ (REF. 144). This fact was established when an anephric patient suffering from sarcoidosis presented with high concentrations of 1,25-$(OH)_2D_3$ and hypercalcaemia[145]. Since then, many reports of hypercalcaemia as a result of ectopic production of 1,25-$(OH)_2D_3$ by granuloma-forming tissue, particularly macrophages, have been published[146].

A recent review provides a summary of diseases in which extrarenal production of 1,25-$(OH)_2D_3$ mediates hypercalcaemia[147], and at least 30 such conditions have been described. The extrarenal production of 1,25-$(OH)_2D_3$ is probably the result of cytokine activation of macrophages participating in the inflammatory process. In this scenario, the expressed 25-OH-D-1α-hydroxylase is insensitive to PTH or to inhibition by 1,25-$(OH)_2D_3$ itself and is not accompanied by the induction of *CYP24A1* expression and, therefore, of the 24-hydroxylase that metabolizes 1,25-$(OH)_2D_3$ (REF. 144). As a result, levels of 1,25-$(OH)_2D_3$ accumulate and lead to toxic effects.

Malignancy. There are many causes of hypercalcaemia due to malignancy[148,149]. Many result from expression of the parathyroid-related peptide by malignant cells[149]. However, hypercalcaemia related to high levels of 1,25-$(OH)_2D_3$ has been described for various lymphomas, for example, Hodgkin's, B-cell and Burkitt's[150]. The mechanisms of expression of the 25-OH-D-1α-hydroxylase in these cases are not entirely clear, but it is likely that the 25-OH-D-1α-hydroxylase expressed in the macrophages in response to interferon-γ and other cytokines may be responsible[144].

Analogues of vitamin D

As described above, several analogues of vitamin D have been developed that are currently used clinically, primarily for the treatment of patients with renal failure, but also for vitamin D-resistant rickets and other disorders (TABLE 2). These analogues have largely appeared not by design but, instead, from obvious chemical modifications and subsequent screening for specific activities.

Of the vitamin D analogues that have been produced, the mechanism by which they are more effective or less effective than the native hormone is not always known. In the case of calcipotriol, which is used topically for the treatment of psoriasis (TABLE 2), its actions can be exerted only on keratinocytes, as calcipotriol has a half-life measured in minutes after it has entered the circulation, which means that it is destroyed before it has had an opportunity to activate calcium absorption and bone calcium mobilization[72]. A similar mechanism is thought to exist for oxacalcitriol[54]. Analogues with the D_2 side chain appear to be less active in activating systems necessary for increasing calcium uptake in the gut and/or increasing serum calcium[52]. Prohormones such as doxercalciferol and alfacalcidol circumvent first-pass effects and have lower calcaemic activities[54]. Falecalcitriol has an increased half-life in the circulation due to its fluorine groups blocking 24-hydroxylase activity[151].

A number of 'non-calcaemic' compounds have been prepared and reported[152–154]. Unfortunately, low calcaemic activity is reported *in vivo* and the non-calcaemic activities are *in vitro* measurements, usually of cellular differentiation. To be sure of selectivity, it is necessary that the compounds are shown to be effective *in vivo* on the particular target in addition to being low in calcaemic activity *in vivo*. For example, 2MbisP is an analogue with a truncated side chain that has very low potency in

intestine and bone but is quite active in PTH suppression, thus exemplifying an analogue of use in treating renal disease but not necessarily bone disease[155].

Designing a compound that is specific for one target versus another does not seem possible at this stage, because the information necessary for this design remains unknown. If the key genes responsible for calcium absorption were as well defined as the genes responsible for bone resorption, screens for compounds that specifically act on bone and not intestine (and vice versa) could be designed. This could indicate the structural features responsible, providing information for the design of novel analogues.

Crystal structures of the ligand-binding domain (LBD) of the VDR were first published by Moras and colleagues[156] and more recently by Vanhooke and colleagues[157]. These structures have revealed that the VDR pocket for the vitamin D hormone is very large and can accommodate a variety of analogues. Although a great deal of modelling work has been reported, so far there has been no clear means whereby the vitamin D analogues can be designed from the crystal-structure pocket[158]. Of some significance is the fact that vitamin D compounds with marked differences in biological activity do not produce a change in the crystal structure of the LBD of the VDR. However, in these studies, the ligand is often twisted to accommodate the crystal structure of the VDR LBD[157,158]. It is, indeed, possible that in solution the ligand can markedly affect the structure of the LBD, which in turn determines whether certain co-activators or co-repressors are bound or may determine whether a gene is transcribed or not. As yet, no structure–activity studies using solution chemistry have been published.

Nevertheless, a bone-selective analogue was developed in the authors' laboratory. This compound increases bone mass and is effective in both bone formation and bone resorption, with minimal effect on intestinal calcium absorption[35,36]. This compound emerged as a result of testing in primary cultures of bone-specific cells and in animal models of osteoporosis, rather than by design. However, the modifications present in this compound do indicate the changes in the vitamin D structure that promote the targeting of bone cells. Probably the most important modification is the epimerization of the C20 carbon atom to the *S*-configuration, together with a two-carbon methylene group, resulting in a compound selective for bone.

Future directions

The vitamin D endocrine system has provided a major new area for the investigation of novel approaches for the prevention and treatment of a wide range of diseases. Already, nine compounds based on vitamin D have been approved for clinical use and are of considerable therapeutic value. Excellent examples are 1α-hydroxyvitamin D_3 in use for both bone disease and secondary hyperparathyroidism of renal failure; doxercalciferol and paricalcitol for renal disease; and calcipotriol for psoriasis.

In the future, it is likely that there will be new compounds available that more specifically target aspects of vitamin D function. The discovery of such compounds will be aided by the identification of key specific genes responsible for the various functions of vitamin D, which could then lead to the identification of components of the vitamin D chemical structure that are important in these functions. With this knowledge in mind, omitting particular functional groups could be one approach for designing selective analogues. It is likely that more efficacious vitamin D analogues selective for bone formation or resorption will be developed. Analogues selective for intestinal calcium absorption will also be developed. With the current status of knowledge, it seems that the development of vitamin D analogues specific for components of the immune system is less promising. Nevertheless, with studies ongoing all the time, the prospect of vitamin D therapeutics for treating diseases beyond metabolic bone disorders seems promising.

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Competing interests statement
The authors declare competing financial interests: see web version for details.

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