Understanding the importance of vitamin D for bone and systemic health

Vitamin D deficiency can result in disorders such as abnormal bone metabolism (osteoporosis and osteomalacia) and reduced muscle function (leading to increased falls). There is increasing evidence that inadequate levels of vitamin D can also contribute to, or exacerbate, cardiovascular disease, type 2 diabetes, cellular dedifferentiation (oncogenesis) and immune derangement.

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Vitamin D is an essential regulator of calcium homeostasis, cellular division and immune function. The active vitamin D metabolite, 1α,25-dihydroxyvitamin D (calcitriol), through its ligand the vitamin D receptor, directly regulates gene expression in a wide variety of vitamin D target cells, and is central to the regulation of vitamin D physiology.[1] Circulating as a hormone, it regulates calcium and phosphate homeostasis. At the cellular level, it acts by suppressing or upregulating gene transcription and altering cell signalling and cellular differentiation.[1]

Vitamin D deficiency can result in disorders such as abnormal bone metabolism (osteoporosis and osteomalacia) and reduced muscle function (leading to increased falls).[2] There is increasing evidence that inadequate levels of vitamin D can also lead to, or exacerbate, cardiovascular disease,

IN SUMMARY

- **Vitamin D is an essential regulator of calcium homeostasis, cellular division and immune function.**
- **Vitamin D deficiency can result in disorders such as abnormal bone metabolism and reduced muscle function. There is increasing evidence that inadequate levels of vitamin D can also contribute to, or exacerbate, cardiovascular disease, type 2 diabetes, cellular dedifferentiation and immune derangement.**
- **Levels of serum 25-hydroxyvitamin D of 50 to 75 nmol/L and above are considered optimal for maintaining good 'overall health'.**
- **Adequate sunlight exposure remains the simplest effective way to maintain vitamin D levels. Exposure of around 15% of the body surface (that is, the hands, face and arms or legs) to around one-third of a minimal erythemal dose of sunlight (the amount that causes faint redness), most days is recommended for adequate endogenous vitamin D synthesis.**
- **In patients with a mild to moderate vitamin D deficiency, supplementation with 3000 to 5000 IU (75 to 125 µg) oral cholecalciferol per day for at least six weeks is recommended.**
- **In patients with severe vitamin D deficiency, higher dosages of vitamin D supplementation (above 5000 IU per day) are usually required.**

type 2 diabetes, cellular dedifferentiation (oncogenesis) and immune derangement (autoimmune disorders such as lupus, type 1 diabetes, rheumatoid arthritis and multiple sclerosis).[1-3] The most compelling evidence for the pleiotropic actions of vitamin D, however, comes from reports linking vitamin D deficiency to higher risks of death from all causes, by mechanisms as yet unknown.[4]

One of the major uncertainties in vitamin D research is the optimal level of serum 25-hydroxyvitamin D (25-OHD) that is required for 'good health'.[5-7] The definitions of vitamin D deficiency as a serum 25-OHD level of below 25 nmol/L and insufficiency as a serum 25-OHD level of between 25 and 50 nmol/L have largely been derived from metabolic bone studies.[8] Optimal levels may be higher, around 75 nmol/L. Healthy individuals who receive adequate sunlight exposure usually have serum 25-OHD levels above 90 nmol/L.[1] This review will focus on some of the clinical evidence linking low levels of serum 25-OHD to a number of diseases that are sensitive to vitamin D, and outlines the importance of maintaining high levels of serum 25-OHD for disease prevention.

Vitamin D metabolism

The main source of vitamin D is its formation endogenously in the skin through exposure to ultraviolet B light (Figure 1).[9,10] Vitamin D can be ingested orally as either plant-derived vitamin D_2 (ergocalciferol) or animal-derived vitamin D_3 (cholecalciferol), which is the type made in the skin. Circulating vitamin D is transported to the liver and converted to 25-OHD. This is the major circulating metabolite, with a half-life of 12 to 19 days. It is converted intracellularly to the highly active metabolite 1α,25-dihydroxyvitamin D, which has a half-life of only a few hours. The enzyme 1α-hydroxylase, which is found in the kidney and a number of other cell types, is crucial to the activation of this pathway and serves as the regulator of calcitriol production.[1,2] Most circulating vitamin D compounds are bound to vitamin D carrier proteins, principally vitamin D binding protein. The affinity of vitamin D binding protein for calcitriol is high, so only a small fraction of the calcitriol circulates in a 'free' form.[1]

Vitamin D metabolites decrease by approximately 40 to 50% in patients after they reach the age of 65 years, resulting in approximately a 40% reduction in calcium absorption. This may occur as a result of age-related factors (such as low dietary intake, diminished sunlight exposure, low previtamin D concentrations in the skin and a decline in renal function) and secondary causes (Table 1).[1,2,10] Serum 25-OHD is the key metabolite reflecting vitamin D stores in the body.

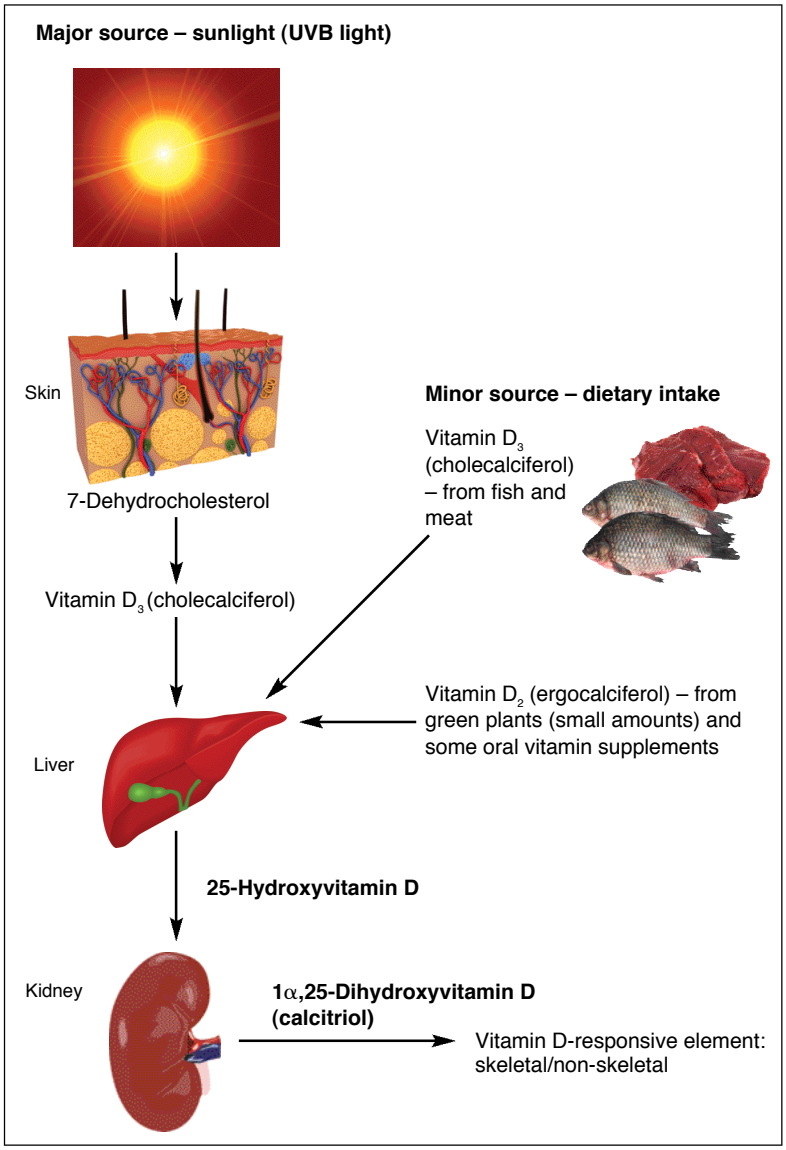

Figure 1. The pathway for vitamin D synthesis and its modes of action.

Bone and muscle

Vitamin D deficiency and fracture risk

Calcitriol facilitates the absorption of calcium, phosphate and magnesium (which together constitute about 90% of the skeleton) from the

Table 1. Causes of vitamin D deficiency

Reduced production or intake of vitamin D

- Low sunlight exposure or availability of ultraviolet B (due to dark skin pigmentation, ageing, veiling, excessive use of sunscreens, chronic illness, avoidance of sun due to chronic skin disorders or cancers)
- Low dietary intake

Reduced absorption of vitamin D from the gut

- Pancreatic and bile duct disorders
- Small bowel disorders – coeliac disease, inflammatory bowel disorders and small bowel resection

Reduced synthesis or enhanced degradation of 25-hydroxyvitamin D

- Chronic liver diseases – hepatitis, cirrhosis
- Chronic anticonvulsant therapies (epilepsy)

Reduced synthesis of 1α,25-dihydroxyvitamin D

- Chronic renal disease

small intestine, maintains calcium homeostasis through this and its interaction with parathyroid hormone, and promotes skeletal mineralisation and bone formation by regulating specific osteoblast gene transcription.[11] It also controls bone turnover and bone remodelling through the receptor activator of nuclear factor-kappaB ligand (RANKL) and osteoprotegerin cytokine system.[11]

A mild deficiency in vitamin D (defined as a serum 25-OHD level of between 25 and 50 nmol/L) is usually associated with secondary hyperparathyroidism and an increase in age-related bone loss.[12] Severe vitamin D deficiency (defined as a serum 25-OHD level of below 12.5 nmol/L) is usually associated with a mineralisation defect.[11] Figures 2a to c show examples of fragility fractures occurring with vitamin D deficiency).[11] A decrease in bone mineral density and an increase in fracture rates have been reported in several cross-sectional studies in individuals with the lowest quartile of serum 25-OHD (in one study this was defined as below 47.5 nmol/L).[13,14]

Vitamin D is also responsible for regulation of muscle function.[2,3] Severe vitamin D deficiency results in a metabolic myopathy.[1] Increases in body sway and quadriceps muscle weakness have been reported in patients with levels of serum 25-OHD below 30 nmol/L.[15] A dose–response relationship between vitamin D status and muscle health has been reported in the National Health and Nutrition Examination Survey (NHANES), with increasing muscle strength continuing through the reference range of 25 to 90 nmol/L of 25-OHD.[15] These findings suggest a link between vitamin D deficiency, falls and an increased risk for hip fracture.

Vitamin D therapy and fracture reduction

Vitamin D and its analogues correct vitamin D deficiency by normalising gut calcium absorption and parathyroid function, establishing normal bone turnover, increasing bone mass and reducing falls and fracture risk.[12-14] The greatest therapeutic effect of vitamin D supplementation has been seen in high-risk individuals with low levels of serum 25-OHD. These individuals demonstrated increases in bone densities ranging from between 0 and 4% in patients who were vitamin D insufficient to between 10 and 40% in those who were vitamin D deficient.[16,17]

Vitamin D therapy has also been shown to improve reflexes and reduce the risk of body sway and falls.[18] In a meta-analysis (three randomised trials, n = 5572), vitamin D supplementation (700 to 800 IU per day) with or without calcium supplementation was associated with a 26% reduction in the risk of sustaining a hip fracture versus calcium supplementation alone or placebo.[19] The musculoskeletal benefits of vitamin D demonstrated in clinical trials may partly be attributed to the combined effect of additional oral calcium supplementation.

Cardiovascular system

Observational studies in humans have demonstrated an inverse relationship between calcitriol and blood pressure or plasma renin levels in normotensive and hypertensive individuals.[20] Two randomised controlled trials have shown that levels of serum 25-OHD of 75 nmol/L or above were associated with the lowest incidence of hypertension over a four-year follow-up period.[21,22] In a recent prospective study of 3258 patients scheduled for coronary angiography, individuals with levels of serum 25-OHD in the lower two quartiles (14 to 42 nmol/L) had an almost doubling in cardiovascular mortality compared with those in the highest quartile.[4]

Reports have also shown that vitamin D therapy not only reduced blood pressure in hypertensive individuals, but also resulted in a 50% lower risk of heart attack and an 80% lower risk of peripheral vascular disease.[23]

Oncogenesis

Vitamin D deficiency and cancer risk

There are a number of cancers that are vitamin D-sensitive, where there is some evidence of an association between low vitamin D and increased risk of, or mortality from the disease. These include cancers of the gastrointestinal tract (colon, oesophageal, gall bladder, gastric, pancreatic and rectal) and urogenital tract (bladder, kidney and prostate), and breast, endometrial and ovarian cancer, as well as lymphoma.[24] Vitamin D inhibits tumour growth by its tumour suppressor action on more than 400 tumour-related genes.[3]

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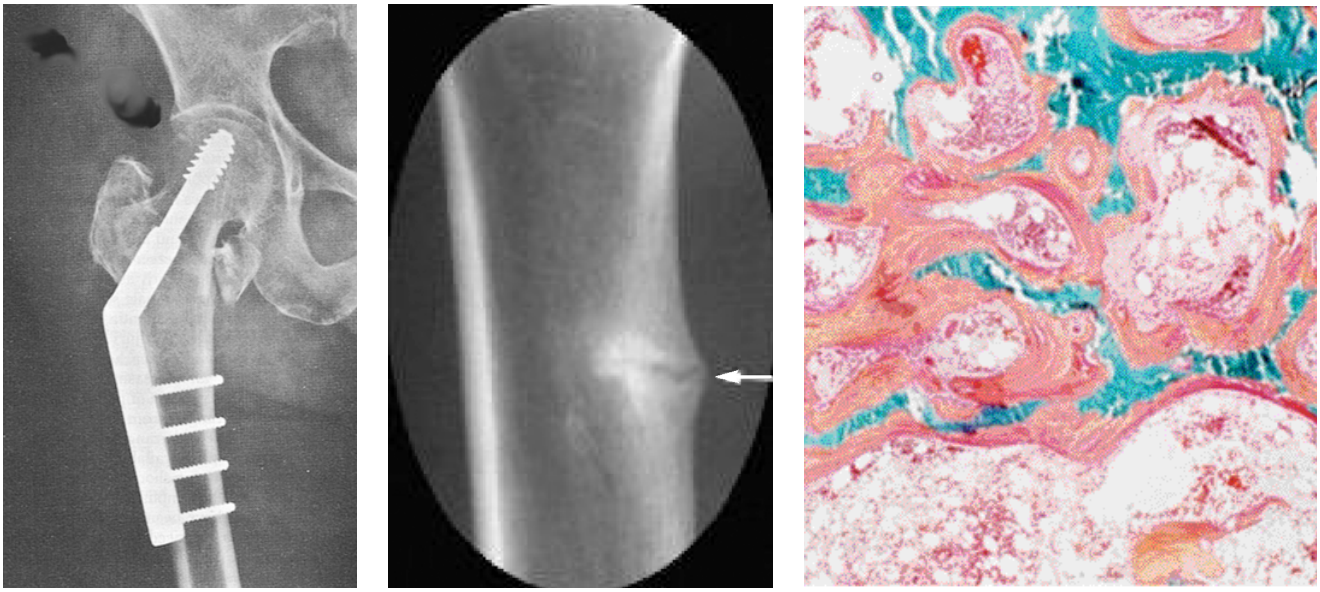

Figure 2. Examples of fragility fractures occurring in patients with vitamin D deficiency. a (left). X-ray of osteoporotic hip fracture treated by surgical stabilisation. b (centre). X-ray of pseudofracture of femoral shaft (also known as Looser zone). c (right) Bone biopsy of classic osteomalacia showing decreased bone volume (blue) and increased osteoid or unmineralised bone (orange).

Individuals who live in regions of the world where sunlight exposure is low (e.g. some countries in the Northern hemisphere)[25] or who have low vitamin D intakes or low levels of serum 25-OHD are at higher risk of developing breast, colon and prostate cancer.[26] Moreover, women with high levels of serum 25-OHD have been shown to have lower mortality rates from breast cancer than those with low levels.[27] In the laboratory setting, animals implanted with tumours have been shown to have lower rates of tumour growth and size when treated with vitamin D.[28]

Vitamin D therapy and cancer risk

There is only one randomised control trial to date relating to vitamin D therapy and cancer risk. In this trial, postmenopausal women (n = 1179) aged over 55 years were randomised to supplemental calcium alone (1400 to 1500 mg daily), supplemental calcium plus vitamin D_3 (1100 IU [27.5 µg] daily) or placebo for four years. During this period, levels of serum 25-OHD increased from 71.8 (+/- 20.0) to 96.0 (+/- 21.4) nmol/L in the calcium plus vitamin D_3 group. All-cancer incidence was reduced by 77%.[29]

Autoimmunity

Cells of the immune system, have receptors for calcitriol as do other nucleated cells.[2] Adequate vitamin D levels appear to be important in immune regulation, in particular in relation to the development of autoimmune diseases such as type 1 diabetes, multiple sclerosis, inflammatory bowel disease and rheumatoid arthritis.[30-32] There is epidemiological evidence for a latitude gradient for multiple sclerosis.[30] The incidence of multiple sclerosis is low in the tropics and increases with distance from the equator in both hemispheres. A lower risk of multiple sclerosis with higher intakes of vitamin D was also reported in studies of over 95,000 nurses.[33]

A Finnish study that examined neonatal records of over 10,000 children found that those who took recommended vitamin D supplements of 2000 IU (50 µg) per day during infancy had one-fifth the risk of developing type 1 diabetes over the next 30 years. Conversely, those infants with suspected rickets had a threefold increase in risk of developing type 1 diabetes over the next 30 years.[32,34]

Although these sorts of studies show association, rather than causation, vitamin D status or supplementation with vitamin D compounds is clearly implicated in modulating the severity and time course of several animal models of autoimmune disease, including type 1 diabetes, inflammatory bowel disease, arthritis and systemic lupus erythematosis.[1-3] Adequate vitamin D status appears to help maintain an appropriate balance between effector cells that destroy target cells and the regulatory immune cells that dampen down the response.[3]

Innate immunity

It has long been suspected that low levels of vitamin D predispose individuals to infections, but this has been difficult to disentangle from other socioeconomic factors and, until recently, was poorly

understood.[35] In 1903, Niels Finsen won the Nobel prize for showing that sun exposure ameliorated cutaneous tuberculosis.[36] It took more than 100 years for the mechanism to be elucidated. *Mycobacterium tuberculosis* activates Toll-like receptors on macrophages, which are part of the innate immune system.[36] This triggers upregulation of the vitamin D receptor and the 1α-hydroxylase enzyme that converts 25-OHD into calcitriol. Provided that there is an adequate level of 25-OHD, it is converted locally into calcitriol. This then acts on the vitamin D receptor to promote the production of antimicrobial peptides (defensins), which kill bacteria.[37] It is unclear at this stage whether this mechanism is important for a broad range of pathogens or only applicable to limited infective agents.

Skin conditions

Calcitriol has an antiproliferative effect on cells, which may partly contribute to anticancer activity. This effect also applies to skin keratinocytes.[38] Calcitriol and, more recently, less calcaemic vitamin D analogues have been used with some success in the hyperproliferative disorder of psoriasis. The observed usefulness of sun exposure in the management of psoriasis may be explained by vitamin D being produced by ultraviolet B radiation and then being converted to the active calcitriol in the skin.[39] There is some evidence, mainly from cell and animal studies, showing that increased levels of calcitriol in the skin may contribute to protection from ultraviolet radiation, particularly by reducing the DNA damage that occurs as a result of sun exposure.[38]

What is a normal serum 25-OHD level?

Adults with an abundant skin surface to sun exposure (e.g. sea rescue life savers) have mostly been shown to have levels of serum 25-OHD above 90 nmol/L. This is very similar to the levels that were likely to be seen in our ancestors who ploughed the fields or hunted in the wild. In contrast, individuals who live in cities and work all day in offices may have serum 25-OHD levels below 50 nmol/L,[40] particularly at the end of winter.

Other individuals at risk of vitamin D deficiency include those with limited sunlight exposure (due to old age and limited mobility), those who live at high latitudes and those who avoid the sun because of chronic skin disorders or cancers. Individuals with a reduced availability of ultraviolet B due to dark skin, pigmentation, veiling or sunscreens, a low dietary intake (although foods provide less than 10% of requirements), malabsorption (due to pancreatic, bile and small bowel disorders, especially coeliac disease) or

Ten important facts relating to vitamin D

- Vitamin D is important for the normal functioning of most cells.
- Vitamin D deficiency results in calcium malabsorption from the gut.
- Chronic vitamin D deficiency results in increased parathyroid hormone activity, liberation of calcium from skeletal bone stores, osteoporosis and increased risk of falls and fragility fractures.
- Patients with serum 25-hydroxyvitamin D levels of less than 50 nmol/L are at risk for fragility fractures.
- People at high risk of vitamin D deficiency include:
  - elderly people
  - people who avoid sunlight due to medical reasons
  - people who are institutionalised or chronically ill
  - people who are modestly clothed (veiled) for religious reasons
  - people who use overzealous amounts of block-out sunscreens (even when there is little or no sun exposure or in winter)
  - people who have dark skin, such as individuals from the Horn of Africa, Middle East and Asia
  - people with secondary medical disorders such as chronic hepatobiliary, coeliac and renal disease
  - obese individuals undergoing bariatric surgery for their metabolic disorder.
- Correcting vitamin D deficiency with optimal therapy reduces risk of fracture by increasing bone strength and reducing risk of falls.
- Serum 25-hydroxyvitamin D levels above 75 nmol/L are considered optimal for maintaining good 'overall health'.
- The principal source of vitamin D is from the action of sunlight (ultraviolet B radiation) on a vitamin D precursor in the skin.
- To be most effective, vitamin D supplements should always be administered with adequate calcium supplements because of a likely combined deficiency.
- The recommended daily vitamin D requirement is controversial, but an intake of 1000 to 2000 IU (25 to 50 µg) per day is considered optimal for all body functions. In patients with a mild to moderate vitamin D deficiency, supplementation with 3000 to 5000 IU (75 to 125 µg) oral cholecalciferol per day for at least six weeks is recommended. Dosages above 5000 IU per day may be required to correct a severe vitamin D deficiency.

continued

other chronic illnesses that impair the synthesis of active metabolites (chronic liver and renal disease) are also at risk of vitamin D deficiency.[2,3,8]

Vitamin D therapy

Adequate sunlight exposure remains the simplest effective way to maintain levels of vitamin D. Exposure of around 15% of body surface (that is, the hands, face and arms or legs) to around one-third of a minimal erythemal dose of sunlight (the amount that causes faint redness), most days, is recommended for adequate endogenous vitamin D synthesis. For people with fair skin, six to eight minutes of sun exposure just before 11 a.m or just after 3 p.m most days in summer, or around 20 minutes at noon most days in the winter (eight to 40 minutes, depending on latitude) should be adequate. Although sun exposure can be used to treat vitamin D deficiency, this has to be balanced against the risk of skin damage.[8-11]

Oral cholecalciferol (e.g. Blackmores Vitamin D_3, OsteVit-D, Ostelin Vitamin D) may be the most appropriate agent to treat vitamin D deficiency. To be most effective, vitamin D supplements should be administered with adequate amounts of calcium supplements because of a likely combined deficiency (combined vitamin D and calcium supplements include Citracal + D, OsteoBlast Absolute Bone Care, and Ostelin Vitamin D & Calcium and Caltrate 600 mg with Vitamin D Tablets).

Calcitriol is not considered ideal for treating patients with simple vitamin D deficiency, in part because of the potential risk of hypercalcaemia. Vitamin D_2 – ergocalciferol – is less effective at raising serum 25-OHD levels, and is therefore generally not used for dietary supplementation.[41]

The daily requirement for vitamin D is probably between 1000 and 2000 IU (25 to 50 μg) per day.[42] A larger dose is probably required for cancer prevention, aiming to maintain levels of serum 25-OHD above 75 nmol/L. Vitamin D enters fat, but whether it can be released from there is unclear.

In patients with a mild to moderate vitamin D deficiency, supplementation with 3000 to 5000 IU (75 to 125 μg) per day oral cholecalciferol is recommended (three to five capsules of oral cholecalciferol 1000 IU per day). At least six weeks of therapy is required to achieve levels of serum 25-OHD above 75 nmol/L. In patients with a moderate to severe vitamin D deficiency, higher dosages of vitamin D supplementation (above 5000 IU per day) are usually required. Higher oral dose formulations (10,000 to 25,000 IU capsules) can be used and are available through local compounding chemists.

Vitamin D (cholecalciferol) can be administered by intramuscular injection to facilitate compliance in elderly patients. Intramuscular injections can be monthly (50,000 IU), four-monthly (100,000 IU), six-monthly (300,000 IU) or 12-monthly (600,000 IU) doses. These dosage regimens are considered safe

provided patients do not have underlying conditions associated with hypercalcaemia. Intramuscular megadose formulations are most beneficial for patients with malabsorption or those with persistent vitamin D deficiency, but are only available through tertiary care hospitals.

Summary

There is now level 1 evidence demonstrating fracture risk reduction in vitamin D-deficient individuals supplemented with optimal vitamin D. Although an association between vitamin D deficiency and numerous medical disorders has been described, there remains a question about its role in direct causality. The box on page 23 lists some important facts relating to vitamin D.

A large-scale, placebo-controlled clinical trial conducted over several years with mortality rates as a primary outcome, in addition to several substudies investigating effects of vitamin D supplementation on other secondary outcomes (including infection, autoimmune diseases, progression of type 2 diabetes mellitus and cancer) is undoubtedly needed. MT

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A list of references is available on request to the editorial office.

COMPETING INTERESTS: Associate Professor Diamond is a scientific advisor to Eli Lilly, Merck Sharp & Dohme, Novartis, Roche, Sanofi-Aventis and Servier, but does not receive financial remuneration. Honoraria for GP lectures and travel grants to attend Local and International Bone Meetings have been received from all the above companies. Professor Mason has received research funding from Servier (France) Nycomed (Germany) and honoraria from Abbot Pharmaceuticals and Blackmores (Australia).

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