Valerie's vitamin D

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The case of a woman with a fragility fracture who is already taking risedronate and calcium is used to review vitamin D deficiency.

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Vitamin D deficiency is one of several common and often unrecognised conditions in older women. This article reviews why it is important to identify patients with this condition and also discusses the management of affected patients.

ACTIVATION OF VITAMIN D

Some vitamin D is supplied by food but the major source is synthesis in the skin under the influence of ultraviolet light. Although synthesis of vitamin D is controlled to some extent in the skin, overall regulation of vitamin D activity occurs in the kidney.

Vitamin D undergoes two activation steps in the body:

- conversion in the liver of vitamin D to the major circulating metabolite 25-hydroxyvitamin D (25-OHD), by the action of vitamin D-25-hydroxylase
- conversion in the kidney of 25-OHD to the highly active metabolite 1,25-dihydroxyvitamin D (1,25-diOHD; also known as calcitriol), by the action of vitamin D-1-hydroxylase.

The other major dihydroxyvitamin D metabolite formed in the kidney, by the action of vitamin D-24-hydroxylase, is 24,25-dihydroxyvitamin D (24,24-diOHD). This has some biological activity but has not been as well studied as 1,25-diOHD.

The regulation of vitamin D activation is controlled by a wide range of factors, but particularly by parathyroid hormone through its effect on vitamin D-1-hydroxylase. In turn, the secretion parathyroid hormone is affected directly by the ionised serum calcium and 1,25-diOHD levels.

Renal 1-hydroxylation is also affected by serum phosphate levels. A low phosphate level increases 1-hydroxylation and the increased 1,25-diOHD level inhibits secretion of parathyroid hormone. This reduces the parathyroid hormone level and thereby reduces renal phosphate loss, and the tendency to hypophosphataemia.

Other hormones affect renal activation at different stages of life, such as growth hormone during periods of growth and certain hormones during pregnancy.

EFFECTS OF VITAMIN D

The active form of vitamin D, 1,25-diOHD, is involved in maintaining calcium homeostasis through its interaction with its target tissues, the bone and intestine.[1] It stimulates the absorption of calcium and phosphate from the small intestine, increasing the serum concentrations of these minerals. It also promotes bone formation and mineralisation and is involved in maintaining neuromuscular function. Circulating 1,25-diOHD regulates bone metabolism partly by stimulating the formation of osteoclasts, which then break down bone and release calcium into the blood.

Effects on bone

Without vitamin D, the protein matrix of bone (osteoid) is laid down but mineralisation is patchy, disorganised and incomplete. Bone is continually turning over, bone resorption usually being balanced by bone formation. In cases of mild to moderate vitamin D deficiency, parathyroid hormone secretion increases to maintain the serum calcium concentration. It does this by:

- increasing calcium absorption from the gut (by increasing conversion of 25-OHD to 1,25-diOHD)
- decreasing renal calcium loss (by increasing renal calcium reabsorption)
- increasing bone turnover and net bone calcium reabsorption.

Both the increased bone turnover and net bone calcium reabsorption increase bone fragility and the risk of fracture.

In cases of more severe vitamin D deficiency, bone formation is abnormal, osteoid is formed but not mineralised, and bone fragility increases.

These effects are first noticed in trabecular bone because this turns over fastest. Fractures occur particularly in the axial skeleton, such as multiple fractures of vertebrae and ribs. A bone scan would show these multiple fractures, many of which will have been asymptomatic. Sometimes malignant deposits are suspected. In these cases, an MRI scan would clearly show the cause of the increased uptake and whether the fracture was recent and associated with oedema, or older. However, no Medicare rebate is available if the patient is referred for the MRI by a GP.

Effects on muscle

Vitamin D deficiency has a number of indirect and direct effects on muscle function. It is associated with decreased gut calcium absorption, secondary hyperparathyroidism and renal phosphate loss.

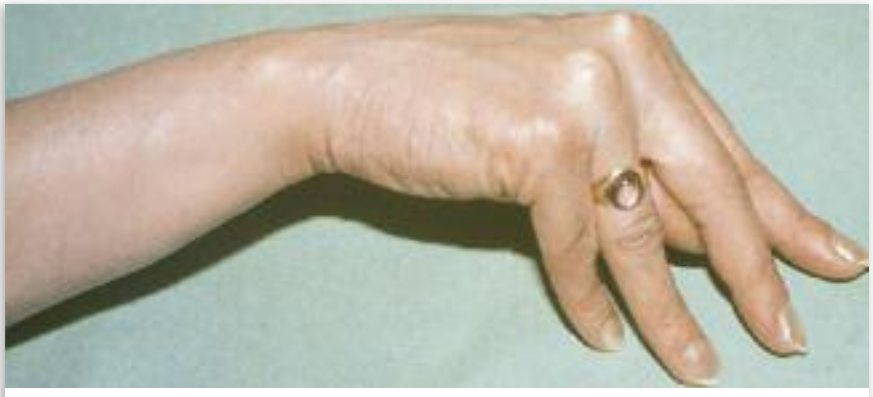


Figure 1. Trousseau's sign, or carpopedal spasm. Mild ischaemia (as from a sphygmomanometer cuff inflated to above systolic blood pressure for three minutes) causes contracture of the flexures of the arms and fingers in patients who have severe vitamin D deficiency.

Figure 2. Chovstek's sign. Tapping over the facial nerve below the zygomatic arch causes the facial muscles to twitch the corner of the mouth in patients with severe vitamin D deficiency.

The phosphate deficiency contributes to the problem of bone mineralisation and, if severe, also results in a range of multisystem problems.

Hypophosphataemia without phosphate depletion (such as occurs during a shift of phosphate from the extracellular to the intracellular compartments during correction of diabetic ketoacidosis) affects the metabolism of the formed elements of blood. Consequently, there may be red cell haemolysis and platelet and white cell dysfunction. In addition to these effects, if total body phosphate is depleted then many organ systems can suffer, including the nervous system and muscle. Muscles become weak and may also be damaged, an extreme case being rhabdomyolysis.

If vitamin D deficiency is severe, hypocalcaemia affects membrane polarisation and depolarisation in excitable tissues such as muscle. The classical signs are carpopedal spasm (Trousseau's sign), where mild ischaemia causes contracture of the flexures of the arms and fingers, and Chovstek's sign, where tapping over the facial nerve below the zygomatic arch causes the facial muscles to twitch the corner of the mouth (Figures 1 and 2).

Apart from these indirect effects, vitamin D and/or its metabolites seem to

have direct effects on muscle and their deficiency is associated with muscle weakness. The combination of abnormal bone mineralisation and muscle weakness explains the high risk of fractures associated with vitamin D deficiency and the benefits of supplements in people who are deficient (see the flowchart on this page).

Other effects on the body

Epidemiologically, vitamin D deficiency is associated with a range of immune problems including type 1 diabetes.[1] Some of the increasing incidence of type 1 diabetes worldwide has been attributed to increasing vitamin D deficiency. The incidence of some cancers may also increase with vitamin D deficiency, possibly through an immune mechanism.[1]

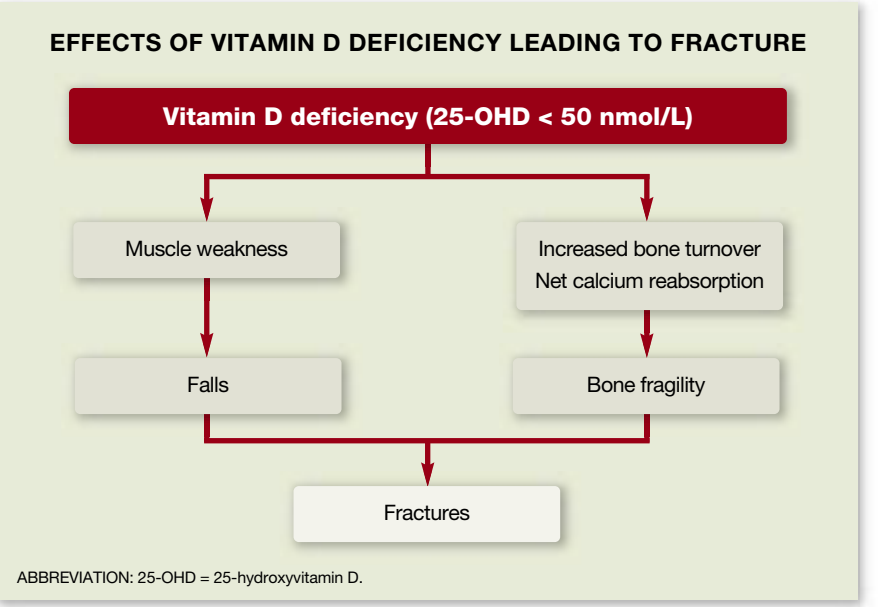
Interestingly, type 2 diabetes and cardiovascular disease are also associated with vitamin D deficiency, but the mechanism remains unclear.[1]

Reversibility of adverse effects of vitamin D deficiency

Some of the primary and secondary effects of vitamin D deficiency are reversible. In children, vitamin D deficiency causes the classic syndrome of rickets where the immature bone bends, resulting in deformities such as bow legs or collapsed pelvis. Even if the vitamin D deficiency is corrected, these deformities remain, leading to later problems such as osteoarthritis of weight-bearing joints (in patients with bow legs) or difficulties with childbirth (in women with a collapsed pelvis).

Fragility fractures in patients with adult osteomalacia also remain more likely, as do any deficits associated with neurological or muscle damage. Haemolysis and rhabdomyolysis cause their own sets of problems, as haemoglobinuria and myoglobinuria potentially cause renal failure.

Both the mineralisation defect and muscle weakness related to vitamin D deficiency are reversible. Vitamin D supplementation in patients staying in residential care, in whom physical frailty already increases the risk of falls and fractures, is associated with a reduction in falls and fractures within the first year of treatment.[2]



CASE SCENARIO

Valerie, who is 62 years of age, has had a fragility fracture at T9 and is taking risedronate 35 mg per week and calcium carbonate 600 mg per day. She would like to know more about vitamin D deficiency.

How common is vitamin D deficiency in Australia?

Vitamin D deficiency is surprisingly common in Australia. The current estimate of the lower limit of an acceptable serum 25-OHD level is 50 nmol/L.[3] However, many believe that ill effects attributable to vitamin D deficiency still occur at higher levels. Even at the currently accepted level, community surveys suggest a prevalence of vitamin D deficiency of 37 to 67% in winter/spring in Australia.[4]

Because virtually all our vitamin D is derived from sun exposure, people at high risk of vitamin D deficiency are mostly those whose sun exposure is decreased (Table 1). There is a smaller group of people who are at risk because of malabsorption of fat and associated malabsorption of exogenous vitamin D and abnormal vitamin D metabolism.

Routine vitamin D and calcium supplementation is often recommended in these groups, particularly for people in residential care where physical frailty already puts them at risk of falls and fractures. Studies have shown reduced rates of fracture in such supplemented groups compared with control groups.[2]

Many doctors would argue that if a person is prepared to take an osteoprotective medication, he or she should seriously consider taking both calcium and vitamin D supplements as well because these were included in most of the trials that demonstrated the effectiveness of osteoprotective medications.

What are the major dietary sources of vitamin D and what affects its absorption?

Dietary intake is only a minor source of vitamin D. Fish and products of fish, especially fish oil, are the main dietary

TABLE 1. GROUPS AT RISK OF VITAMIN D DEFICIENCY[3]

- Elders in residential care
- Elders admitted to hospital
- Patients with hip fractures
- Dark skinned people (especially veiled)
- Mothers and infants with rickets

TABLE 2. SUN EXPOSURE REQUIRED FOR ADEQUATE VITAMIN D SYNTHESIS IN FAIR PEOPLE[3]*

Region	Summer (minutes)	Winter (minutes)
Cairns	6–7	9–12
Brisbane	6–7	15–19
Sydney	6–8	26-28
Perth	5–6	20–28
Adelaide	5–7	25–38
Melbourne	6–8	32–52
Hobart	7–9	40–47

* Sun exposure times at 10.00 a.m. or 2.00 p.m. (no daylight saving) resulting in one-third minimal erythemal dose. Exposure times for people with more pigmented skin would be higher.

SOURCE: Derived from data in reference 3.

source in Australia (this is the animal-derived form, vitamin D_3, which is also known as cholecalciferol). Although dairy products are often considered to be good sources of vitamin D, this is only true in countries such as the USA that supplement food with vitamin D; such supplementation does not occur in Australia. Very small amounts of the plant-derived form of the vitamin, vitamin D_2 (also known as ergocalciferol) are obtained from green vegetables.

Being derived from cholesterol, vitamin D is absorbed in the same way as fat, requiring bile to make it soluble and an intact distal small bowel for absorption. Gastrointestinal malabsorption reduces the absorption of dietary vitamin D but also, for some as yet unclear reason, affects vitamin D metabolism and reduces circulating levels of vitamin D.

How important is sunlight exposure in providing vitamin D?

People in Australia derive almost all their vitamin D from its formation in the skin through the conversion by ultraviolet B radiation of a precursor, dehydrocholesterol, into vitamin D_3. Exposure to sunlight is therefore important for achieving adequate vitamin D levels.

Although Australia is a 'sunburnt country', these days it is becoming progressively sunblocked as well. The country's 'slip, slap, slop' campaign that encourages people to 'slip on a shirt, slop on sunscreen and slap on a hat' to prevent skin damage from ultraviolet light also blocks the ultraviolet rays needed to produce vitamin D_3. This is a particular problem in people belonging to cultures that require most of the body to be covered with clothing and in those with dark skin colouring (melanin blocks ultraviolet light and reduces skin damage but at the same time decreases vitamin D_3 synthesis).

How much sunlight is enough to produce adequate vitamin D?

The amount of sun exposure required for adequate vitamin D production depends on the latitude and the time of year. This is obvious at the extremes, such as high latitudes where ultraviolet rays are more attenuated by the longer, angled atmospheric path of sunlight and where sunlight duration varies dramatically with the season. However, the effects of latitude and season are generally underestimated in Australia.

Exposure of the face, hands and arms or legs to about one-third of the individual's minimal erythemal dose of sunlight (the minimal erythemal dose is the amount that would cause faint redness) on most days is sufficient for adequate vitamin D synthesis.[3] For people with moderately fair skin, this would be about 11 minutes in Cairns compared with about 43 minutes in Hobart in the winter months, and about six minutes in Cairns compared with about eight minutes in Hobart in the summer months (Table 2).

In summer, it is easy to get enough sunlight exposure for adequate vitamin D production. In winter, however, it is considerably more difficult in the southern parts of Australia, where most of the population lives. Moreover, people cover up more in winter, and may not venture outdoors as much.

What medications affect vitamin D metabolism?

Medications can affect all stages of vitamin D metabolism, acting either directly or indirectly (Table 3). The effects can become important when calcium and/or vitamin D levels are already compromised (such as in patients with hyperparathyroidism or vitamin D deficiency).

The risk posed by medication may not be recognised in patients with primary hyperparathyroidism in whom parathyroidectomy is deferred. Parathyroid hormone secretion is autonomous and 1,25-diOHD levels are high despite hypercalcaemia. Renal calcium loss provides a route of elimination for calcium, but thiazide diuretics increase renal

calcium reabsorption and can thereby cause serum calcium levels to dramatically increase, especially in patients with impaired renal function.

Similarly, a marginal state of vitamin D deficiency could be unmasked by the taking of a medication such as orlistat that reduces gastrointestinal absorption of fat and fat-soluble vitamins (including vitamin D), or an anticonvulsant such as phenytoin, which accelerates the hepatic metabolism of 25-OHD to inactive metabolites.

TABLE 3. MEDICATION EFFECTS ON VITAMIN D METABOLISM

Medication	Mechanism
Direct effects	
Orlistat	Decreased vitamin D absorption
Anticonvulsants	Increased liver 25-OHD catabolism
Calcitriol	Provides exogenous 1,25-diOHD
Indirect effects	
Calcium antacids or supplements	Increased calcium availability, decreased parathyroid hormone, decreased renal 1-hydroxylation
Magnesium trisilicate/ aluminium hydroxide antacids	Decreased phosphate absorption, increased renal 1-hydroxylation
Thiazides	Decreased calciuria, increased calcium availability, decreased parathyroid hormone, decreased renal 1-hydroxylation

ABBREVIATIONS: 1,25-diOHD = 1,25-dihydroxyvitamin D; 25-OHD = 25-hydroxyvitamin D.

CASE SCENARIO CONTINUED...

Valerie asks if she should take a vitamin D supplement, as do some of her friends.

Should people such as Valerie routinely take vitamin D supplements?

There is no consensus about whether people such as Valerie should routinely be given vitamin D supplements or whether supplementation should be limited to those with demonstrated vitamin D deficiency. There is a continuum from vitamin D supplements clearly being indicated to clearly not being required. Osteoporosis and fragility fractures can occur in otherwise healthy older people who enjoy an active outdoor life as well in as those confined to bed in residential care.

As noted earlier, a case can be made that if osteoprotective medication is prescribed, a co-prescription of vitamin D and calcium supplements should be provided. Moreover, people who are vitamin D replete today may become vitamin D deficient in the future, increasing their bone fragility and muscle weakness.

A reasonable approach with a patient such as Valerie would be to:

- have a low threshold for testing and/or prescribing vitamin D
- keep reviewing vitamin D supplementation in light of the patient's bone fragility
- reconsider the situation when reviewing the osteoprotective medication and the bone density response to the treatment.

If Valerie's 25-OHD level was 40 nmol/L, would 1000 IU of vitamin D per day be enough?

As a rough guide, 1 µg of vitamin D_3 equals 40 IU and 1 µg/day results in a 1 nmol/L increase in 25-OHD levels. In Valerie's case, 1000 IU a day will increase her 25-OHD level by 25 nmol/L (1000 ÷ 40) to a total of 65 nmol/L, which is above the lower recommended level of 50 nmol/L. Different pathology laboratories have different recommendations for target serum 25-OHD level but the current recommendation of the Australian and New Zealand Bone and Mineral Society, the Endocrine Society of Australia and Osteoporosis Australia is at least 50 nmol/L.[3]

Clearly there will be people who require more than 1000 IU of vitamin D per day. Indeed, this may apply to Valerie in the future, when her circumstances change and she has less exposure to sunlight.

VITAMIN D SUPPLEMENTATION

Differences between vitamins D_2 and D_3

The physiological effects of vitamin D_2 are similar to those of vitamin D_3. Some authorities believe that vitamin D_3 may be more effective, but this difference is not dramatic.

More important is the fact that some 25-OHD assays detect mainly vitamin D_3. This is relevant when monitoring vitamin D supplementation to ensure that enough is given and absorbed. Until recently, vitamin D supplements were specifically vitamin D_2 – ergocalciferol. Unsurprisingly, when vitamin D_3 assays were used to assess the adequacy of vitamin D_2 supplementation, there were problems interpreting the results. Recently vitamin D_3 supplements – cholecalciferol – have become available.

Preparations of vitamin D available in Australia

Both ergocalciferol and cholecalciferol supplements are available in Australia. The usual supplemental dose of

cholecalciferol is 1000 IU daily. It is important to note that people who take a supplement with ergocalciferol as the active ingredient may obtain the desired therapeutic effect but their serum levels of the vitamin will not be accurately assessed by the 25-OHD assays that mainly assess vitamin D_3 status.

Often the choice of a cholecalciferol supplement will be guided by price, availability and the need for calcium supplementation (when the cholecalciferol and calcium combination products may be preferred). Cholecalciferol and calcium are also included in some formulations of the bone protective medications alendronate and risedronate. Small amounts of cholecalciferol are also available in multivitamin formulations.

A formulation of high-dose vitamin D (1.25 mg, 50,000 IU) is available through the Special Access Scheme. Other formulations can be prepared by pharmacists. The need for such preparations may be associated with other issues, and advice from a physician with a special interest in vitamin D metabolism might be useful.

A recent retrospective meta-analysis suggested an increased risk of cardiovascular events in women taking calcium supplements without co-administered vitamin D.[5] However, this meta-analysis has been criticised and the findings have not yet been confirmed by prospective trials.

Role of 1,25-diOHD – calcitriol – as a supplement

Calcitriol is used to treat or prevent hypocalcaemia in patients with renal or parathyroid gland impairment but has a limited role in other circumstances. It is subsidised on the PBS for the treatment of hypoparathyroidism, the treatment of hypocalcaemia due to renal disease and the treatment of established osteoporosis in patients with a fragility fracture.

Its use bypasses the need for hepatic and renal activation of vitamin D. This is particularly valuable in patients with renal damage when there may be too little functional tissue to activate enough vitamin D and when high phosphate levels inhibit the capacity that does remain.

The bypassing of renal metabolism has major disadvantages however. The ability to control physiologically this key step in vitamin D metabolism is lost. Usually hypercalcaemia would decrease parathyroid hormone secretion and thereby reduce renal 1-hydroxylation, but this is no longer possible. If the patient takes too large a dose of calcitriol or supplemental calcium, severe hypercalcaemia can occur. Monitoring serum calcium levels is especially important in these patients.

For patients with inadequate vitamin D production or severe fat malabsorption, calcitriol might at first sight appear attractive because it has direct effects on gut calcium absorption. However, calcitriol is usually not used because of the disadvantage of bypassing the control step and also because other metabolites of vitamin D may well have beneficial effects.

Monitoring the adequacy and toxicity of supplements

Although the physiological consequences of vitamin D deficiency can be monitored, this is less sensitive than monitoring serum 25-OHD levels. Calcium, phosphate, bone and mineral metabolisms are significantly abnormal by the time abnormalities are detectable in serum levels of calcium, phosphate, bone alkaline phosphatase and bone turnover markers, or in bone density or muscle function.

One approach is to give enough vitamin D (2000 IU [50 µg] per day) to ensure that recommended levels are achieved, irrespective of endogenous production or dietary sources. Even then, the most common reason for lack of effectiveness – lack of adherence – applies. As for all medications, vitamin D supplements do not work if they are not taken.

CONCLUSION

Vitamin D is involved in calcium homeostasis in the body. Deficiency of this vitamin leads to calcium malabsorption in the gut, disorganised and incomplete bone mineralisation, and muscle weakness, which in combination can lead to falls and fragility fractures, especially in the elderly. Almost all a person's vitamin D is derived from sunlight, and in a sunny climate such as that of Australia, only a short exposure (about five to 20 minutes a day, depending on season and latitude) is required to give adequate serum levels. Oral cholecalciferol is the preferred agent to treat vitamin D deficiency, and is usually taken in combination with a calcium supplement. MT

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