VITAMIN D: MIRACLE CURE-FOR-ALL OR CART BEFORE THE HORSE?

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Marietjie Herselman was born in the Langkloof, where she matriculated at the McLachlan High School. She obtained a BSc (Physiology and Dietetics) degree at Stellenbosch University and for the next 18 years worked as a dietitian at Tygerberg Hospital, where she specialised in renal nutrition. She obtained a master's degree in nutrition in 1985 and in 1991 was appointed as a lecturer in the Department of Human Nutrition, Faculty of Health Sciences, at Stellenbosch University. In the same year she obtained her PhD in nutritional sciences at this university, where she was later promoted to senior lecturer (1995), associate professor (2001) and full professor (2010). From 2008 to 2010 she was appointed first as acting head and later as head of the Division of Human Nutrition.

She served on the Professional Board of Dietetics from 1998 to 2003 and also on various sub-committees of the Board. She regularly reviews papers and research applications for scientific councils/associations as well as five national and four international scientific journals. Currently, she serves on the editorial boards of four international scientific journals and in 2008 she was elected as the co-editor (Africa region) of the international journal Nutrition.

She successfully delivered 17 master's students and published 29 scientific papers in national and international journals and three chapters in textbooks. Marietjie also presented papers at 19 international and 37 national conferences. Three international and four national awards were bestowed on her for her research in renal nutrition. She played a leading role in the initiation of the Community Nutrition Security Project (CNSP) in the Breede Valley, as part of Stellenbosch University's HOPE Project, as well as the NOMA master's programme in Nutrition, Human Rights and Governance in collaboration with the universities of Oslo and Akershus (Norway) as well as Makerere and Kyambogo (Uganda).

VITAMIN D: MIRACLE CURE-FOR-ALL OR CART BEFORE THE HORSE?

WHAT IS THE CURRENT HYPE AROUND VITAMIN D?

During the last decade, there has been an explosion of interest in the 'sunshine vitamin' as scientists started to suggest that the effect of vitamin D in the body extends far beyond its role in healthy bones. At the same time, the sales of vitamin D supplements skyrocketed in developed countries, as indicated by a statement from Jamieson Laboratories, Canada's largest supplement maker: "The nutrient is flying off pharmacy shelves in amounts that are astonishing players in the nutritional supplement business" and "vitamin D sales eclipsed those of vitamin C for the first time ever … capping a year of huge growth for the product".[1] Similarly, the number of laboratory tests for vitamin D has increased exponentially, from approximately 4 000 samples per month in 2004 to 50 000 samples per month in 2008 in just one laboratory.[2] Vitamin D testing has been described as the fastest-growing test in medical laboratories in the USA and other developed nations across the globe due to an unprecedented demand. The cause of this increased demand for vitamin D supplements and testing is the press coverage of reports of a high prevalence of vitamin D deficiency, as well as the steady flow of scientific publications that link vitamin D deficiency with a growing number of medical conditions.[3] There is currently much confusion among health professionals and consumers as a result of conflicting information on the health benefits of vitamin D and dietary requirements.

HISTORICAL PERSPECTIVE

Rickets was first described in the mid 1600s and the condition became more common in the 18th century. By the 19th century it was epidemic in Europe, as more and more families moved from their farms to work in factories in the smoggy air of industrial cities. Very little progress was made during the 19th century to cure the condition and it took nearly three centuries before the anti-rachitic substance was identified as vitamin D in 1922 (Table 1).[4]

Vitamin D is a generic term representing two chemical forms, vitamin D2 (*ergocalciferol*) and vitamin D3 (*cholecalciferol*), which differ only in the chemistry of the side chains. These differences do not affect the metabolism of vitamin D to any great extent, except that vitamin D2 may be metabolised more rapidly than vitamin D3. In general, they have comparable responses in the body.[5] Vitamin D2, which can be produced by ultraviolet B irradiation of ergosterol (found naturally in yeast and sun-exposed mushrooms), was chemically characterised in 1932, with vitamin D3 following in 1936 when researchers discovered that it was synthesised by ultraviolet irradiation of 7-dehydrocholesterol in the skin.[6] An important development was that 1,25-dihydroxyvitamin D [1,25(OH)2D], the active form of vitamin D, was reclassified as a hormone (more specifically a seco-hormone) responsible for the regulation of calcium metabolism.[7] The next important landmark, in the 1970s, was the discovery of a vitamin D receptor that binds 1,25(OH)2D to the nucleus of cells – including cells that do not form part of the classical target tissues responsible for calcium maintenance.[4] Today there is evidence of biological responses in the immune system, pancreas and the cardiovascular, muscle and brain systems, in addition to the intestines and bones.

Table 1: *Selected timelines in the history of vitamin D[4,6,8]*

Mid 1600	Rickets is first described
1827	French researcher reports cures among those given cod liver oil.
1919	Researcher cures children of rickets using artificially produced ultraviolet light.
1920s	Researchers discover that irradiating certain foodstuffs with UV light renders those foods anti-rachitic.
1921	Researchers show that by simply exposing rachitic children to sunlight, they are able to cure them of the disease.
1922	Researcher destroys vitamin A in cod liver oil and calls the separate anti-rachitic substance that remains 'vitamin D'.
1936	Researcher deduces chemical structure of vitamin D3 produced in the skin and identifies structure of 7-dehydrocholesterol.
1968	Researchers isolate an active vitamin D metabolite and identify it as 25-hydroxyvitamin D3, produced in the liver.
1969	Discovery of the nuclear receptor for 1,25(OH)2D3.
1970	Researchers discover the relationship of vitamin D to the body's endocrine system and calcium regulation.
1971	Chemical/molecular structure of 1,25(OH)2D3 is identified and reclassified as a hormone controlling calcium metabolism.
1980	Researchers demonstrate that topical application of the vitamin D hormone is an effective treatment of psoriasis.
1980-	Evidence that a vitamin D receptor is present in over 30 target tissues of man.
1980-	Discovery of 1,25(OH)2D-mediated rapid responses.
1994	US Food and Drug Administration approves a vitamin D-based topical treatment for psoriasis.
2000	First X-ray structure of the VDR ligand-binding domain reported.
2004	Identification of an alternative ligand-binding pocket in the VDR.

THE HANDLING OF VITAMIN D BY THE BODY

After entering the circulation, vitamin D2 and D3 are transported by vitamin D-binding protein to the liver, where they are hydroxylated by one or more cytochrome P450 vitamin D 25-hydroxylases (primarily CYP2R1) to 25-hydroxyvitamin D (25(OH)D), the most abundant and stable metabolite of vitamin D in the blood and generally accepted as the functional indicator of vitamin D status (Figure 1).[9,10] It is the precursor to the only active form of vitamin D (1,25(OH)2D), which is synthesised mainly in the kidneys under the control of cytochrome P450 mono-oxygenase 25(OH)D 1α-hydroxylase (CYP27B1).[10] Then 1,25(OH)2D serves as a ligand that binds with high affinity to the steroid hormone nuclear receptor for 1,25(OH)2D (VDR)[9,11] in cells to form a complex that influences the transcription and transrepression of multiple genes in target tissues. When the VDR is activated, it transcribes the gene for the P450 enzyme (24-hydroxylase or CYP24A1) that metabolises 1,25(OH)2D into inactive products as a feedback control mechanism. Another feedback mechanism limits the amount of 25(OH)D converted to 1,25(OH)2D by 24-hydroxylase (CYP24A1).[10,12]

The presence of VDRs in tissues that are not involved in mineral ion homeostasis led to the discovery of a number of other roles of vitamin D hormone.[13] In its endocrine role, 1,25(OH)2D is released in the blood stream as a hormone with effects in other parts of the body. Its primary target is the intestinal mucosa, where it plays a role in the calcium transport system.[9,11] Should the need arise to absorb more calcium, the synthesis of 1,25(OH)2D is tightly controlled with up-regulation via serum parathyroid hormone (PTH), while synthesis is down-regulated by fibroblast growth factor 23 (FGF23) produced by the osteocytes.[10,14] TThe VDR is also present in many other tissues of the body (Table 2) where it may generate certain biological responses.[15]
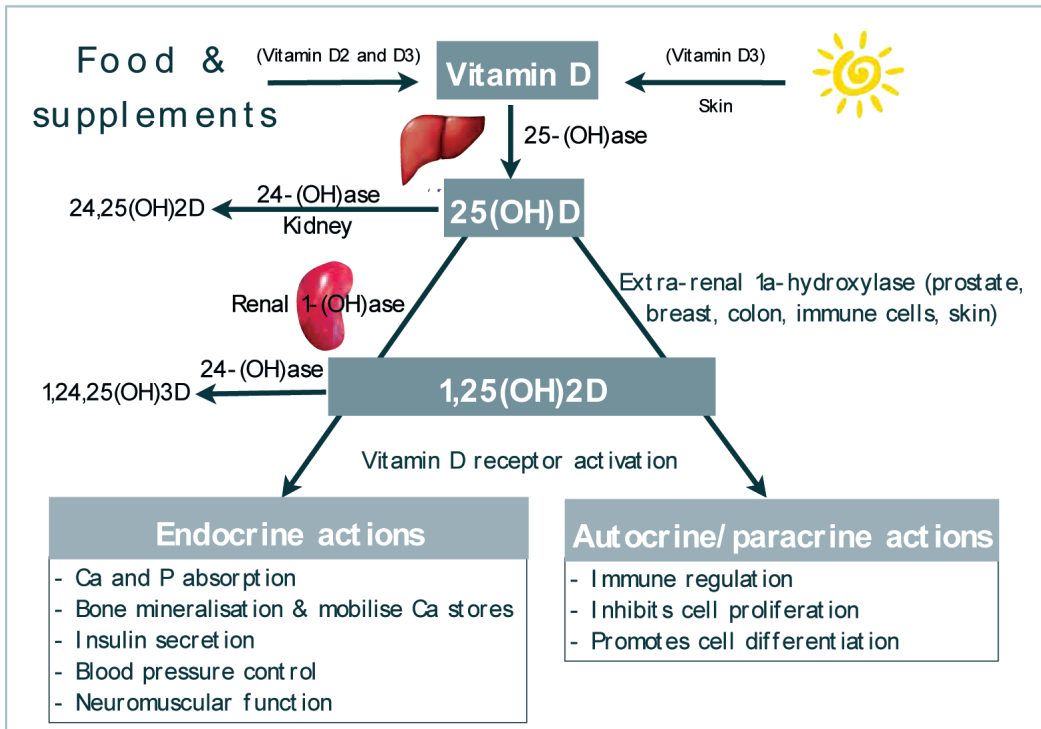
Figure 1: Schematic overview of vitamin D metabolism and function[5,10,13]

Table 2: Distribution of vitamin D receptors in tissues[15]

System	Tissue and cell
Gastrointestinal	Oesophagus, stomach, intestine
Musculoskeletal	Osteoblasts, chondrocytes, striated muscle
Endocrine	Parathyroid, pancreatic ß cells, thyroid C cells
Renal	Tubules, juxtaglomerular apparatus (renin), podocytes
Cardiovascular	Arterial smooth muscle cells, cardiac myocytes
Immune	T cells, B cells, bone marrow, thymus
Hepatic	Liver parenchymal cells
Reproductive	Testis, ovary, uterus
Respiratory	Lung alveolar cells
Epidermis	Keratinocytes, hair follicles
Central nervous system	Brain neurons

As opposed to the endocrine pathway, it is now known that. vitamin D also acts through an autocrine pathway. This means that the hormone binds to receptors on the cells locally where it is produced and affects the function of those cells. To date, 1α-hydroxylase has been identified in many extrarenal cells and tissues, including the prostate, breast, colon, lung, pancreatic β-cells, monocytes and parathyroid cells, where it converts 25(OH)D to 1,25(OH)2D intracellularly.[11] The regulation of 1α-hydroxylase at these sites is different from that in the kidney, as 1,25(OH)2D synthesis and degradation are under the control of local factors (e.g. cytokines and growth factors) aimed at the establishment of optimal levels of 1,25(OH)2D for cell-specific actions. This local pathway is dependent on adequate levels of circulating 25(OH)D, which may explain the association of vitamin D deficiency with diseases such as cancer.[13] These cells also produce vitamin D 24-hydroxylase (CYP24A1), which degrades excess 1,25(OH)2D intracellularly to prevent excess accumulation.[10]

This new knowledge about the complex physiological roles of vitamin D has rekindled interest in the 'sunshine vitamin' and has led scientists to pursue many new applications for vitamin D, especially following reports of vitamin D deficiency in many parts of the world.

SOURCES OF VITAMIN D

It is no coincidence that vitamin D is called the 'sunshine vitamin'. The best source of vitamin D is exposure of the skin to ultraviolet B (UVB) radiation with wavelengths of 290–315 nm, which leads to vitamin D3 being synthesised in the skin from cutaneous 7-dehydrocholesterol (provitamin D3). UVB radiation leads to rearrangement of the double bonds and opening of the B ring of provitamin D3, resulting in a less rigid previtamin D3.[16] Peak synthesis of vitamin D occurs at wavelengths of 295–297 nm, but this quality of light is found mainly in the tropical and subtropical climates and rarely in the arctic regions. Any excess vitamin D3 produced in the skin is converted to inactive products, which protect against toxicity due to excessive exposure to sunlight.[11] Exposure of the body (in bathing suits) to UVB radiation until slight redness of the skin occurs will release 10 000–20 000 IU of vitamin D3 into the circulation.[17] The minimum amount of vitamin D required to maintain serum 25(OH)D in the optimal range is 1 000 IU.[18] This translates into exposure of the arms and legs to sunlight for 5 to 30 minutes between 10:00 and 15:00 in the spring, summer and fall, depending on skin pigmentation, latitude, season, clothing, the use of sunscreen and age.[9] Usually, exposure twice a week is enough to produce sufficient amounts of vitamin D.

Natural food sources of vitamin D are scarce and it is difficult to achieve optimal serum levels of vitamin D by diet alone. The best food sources of vitamin D are fatty fish (such as salmon, tuna, herring, sardines and mackerel) and fish liver oils (cod liver oil), but small amounts are also found in butter, egg yolk and liver (Table 3). Vitamin D in these foods is primarily in the form of vitamin D3.[9] Natural vitamin D2 is found primarily in fungi, mushrooms and algae. Breast milk is a poor source of vitamin D, especially if the mother is vitamin D deficient. It is estimated that an average consumption of 750 mL/day of breast milk without exposure of the infant to sunlight will provide only 11–38 IU of vitamin D per day, which is much lower than the dietary reference intake.[16,19]

Dietary supplements and foods fortified with vitamin D are important sources of dietary intake. Both vitamin D2 and vitamin D3 are suitable for supplements and food fortification.[5,16] In most developing countries, however, the availability of foods fortified with vitamin D is not very reliable. Non-compliance of industry with vitamin D-fortification regulations[20,21] may result in under- or over-fortification of foods, as has been reported in the USA in the nineties. Variations in fortification procedures such as storage of the vitamin preparation, method used for adding vitamin D and the timing at which point the vitamin D is added may further add to variation in the vitamin D content of fortified foods.[21] There is a limited number of food vehicles suitable for vitamin D fortification. These include margarine and dairy products,[22] but orange juice and breakfast cereal have also been fortified.[23] Policymakers should however take note of the outbreak of vitamin D intoxication in infants in the 1950s in Europe, which was believed to be the result of over-fortification of milk and which resulted in laws to stop the fortification of foods with vitamin D.[24] Researchers now believe that this outbreak may have been caused by the presence of CYP24A1 mutations, which have been linked with increased sensitivity to vitamin D. The presence of this mutation is a genetic risk factor for the development of symptomatic hypercalcaemia and it can be triggered by vitamin D prophylaxis in otherwise healthy infants.[25]

Vitamin D supplements are relatively cheap and widely available, either as multiple-vitamin preparations, combined with calcium, or as stand-alone vitamin D supplements. Doses commonly range from 400 IU to 50 000 IU (primarily vitamin D3), and are available in various formulations such as tablets, capsules, liquid drops or chewables. Vitamin D3 has been shown to be more potent than vitamin D2 and to stay in the circulation longer than vitamin D2,[26] but recent reports suggest that the two forms of vitamin D are equally effective in maintaining serum levels.[18] There is however considerable variation in the way individuals respond to vitamin D supplementation and the only way to monitor efficacy and safety of intervention is to measure serum 25(OH)D.[9]

Table 3: *Examples of best sources of vitamin D in South Africa[23,27]*

Source	Amount (IU)
Natural food	
Salmon, 100 g	520
Sardines/pilchards, 100 g	280–320
Mackerel, 100 g	250
Tuna, 100 g	200–280
Herring, 100 g	1 040
Cod liver oil, 1 teaspoon	400–500
Egg, 1 whole	158–168
Exposure to sunlight, UVB (0,5 MED)*	**3 000 IU**
Fortified food	
Margarine, 1 teaspoon	10
Milk powder, 10 g	~35
Infant formula, 240 ml	~100
Breakfast cereal, 50 g	60–135
Supplements	
Vitamin D3	400–50 000

* Approximately 0,5 MED of UVB radiation would be absorbed after 5 to 10 minutes of exposure of the arms and legs to direct sunlight, depending on the time of day, season, latitude and skin sensitivity.

in vitamin D3 synthesis due to absorption of UVB radiation)[11]

- Higher latitudes (most vitamin D is formed at latitudes between 40°N and 40°S) due to greater scatter and absorption of UVB radiation.[32] In winter, above 37°N the number of UVB photons reaching the earth is decreased by 80 to 100%.[17]
- Season (during winter fewer UVB photons strike the earth)[33]
- Ageing (reduction in amount of 7-dehydrocholesterol in the skin; elderly people produce up to 75% less vitamin D3)[34]
- Amount of body fat (sequestration of vitamin D in adipose tissue)[35,36]
- Poor intake of vitamin D (includes natural food, fortified foods or vitamin D supplements, and exclusive breastfeeding)
- Medical conditions interfering with the metabolism of vitamin D (e.g. kidney failure, liver disease and malabsorption syndromes)

POTENTIAL CAUSES OF VITAMIN D DEFICIENCY

The causes of vitamin D deficiency can be linked to decreased synthesis in the skin, decreased intake and certain medical conditions. The causes include the following:

- More time spent indoors
- The use of sunscreen for protection against cancer (95% to 98% decrease in synthesis of vitamin D3 in the skin)[28]
- Amount and type of clothing (a fully clothed infant without a hat will need approximately two hours' exposure to UVB radiation per week compared to 30 minutes per week for an infant wearing only a diaper,[29] and women and children who wear traditional outfits that cover the face and body are at risk of vitamin D deficiency)[30]
- Air pollution and overclouded sky[31]
- Amount of melatonin in the skin (up to 99% decrease

DIAGNOSIS OF VITAMIN D DEFICIENCY

Serum 25(OH)D is the major circulating metabolite of vitamin D with a half-life of 10–19 days and only a fraction of 25(OH)D is converted to 1,25(OH)2D.[16,17] A systematic review of 36 randomised controlled trials (RCTs) and four before–after studies showed that serum 25(OH)D is a robust and reliable biochemical marker of vitamin D status, responding to improved vitamin D status across heterogeneous population subgroups and irrespective of whether calcium is supplemented or not.[37] While total 25(OH)D level is used for the diagnosis and monitoring of vitamin D deficiency, it is suggested that 25(OH)D2 and 25(OH)D3 fractions be used to monitor response to vitamin D2 or D3 supplementation.[38] It is recommended that the measurement of serum levels of 25(OH)D be reserved for individuals at risk of deficiency because of the following:[38,39,40,41,42]

- Renal and liver disease
- Osteomalacia, osteopenia and osteoporosis

- Rickets
- Malabsorption syndromes
- Hypo- or hypercalcaemia/hyperphosphataemia
- Parathyroid disease
- Granulomatous disease
- Sarcoidosis
- Lymphoma
- Patients on medication that affect vitamin D metabolism (glucocorticoids, antiseizure medications, antiretroviral drugs, antifungals, cholestyramine)
- Unexplained increased levels of serum alkaline phosphatase
- Patients taking high doses of vitamin D (> 2 000 IU daily) for more than six months or having symptoms of hypervitaminosis D
- Pregnant and lactating women
- Older adults with a history of falls or non-traumatic fractures
- Malnourished patients (including obese children and adults)
- Limited sun exposure

Serum 1,25(OH)2D, the active form of the vitamin with a half-life of only four hours, is not a good marker of vitamin D deficiency because the level of 1,25(OH)2D in the blood is usually normal or elevated in the presence of a vitamin D deficiency. This is because even subtle decreases in serum calcium due to vitamin D deficiency will lead to a corresponding increase in PTH, stimulation of 1α-hydroxylase and conversion of 25(OH)D to 1,25(OH)2D.[16] Measurement of serum 1,25(OH)2D should therefore be limited to cases suspected of having renal 1α-hydroxylase deficiency (i.e. chronic kidney disease), those with primary hyperparathyroidism, sarcoidosis, oncogenic osteomalacia, vitamin D-resistant rickets[43] and hypercalcaemia with low levels of 25(OH)D.[39] It has been suggested that one should control for serum albumin levels when interpreting serum 25(OH)D, as the latter is transported in the blood bound to vitamin D-binding protein and albumin.[44]

Traditionally, serum 25(OH)D levels of 27,5 nmol/L and 30 nmol/L have been used as the cut-off point for adequacy in children and adults respectively, but in recent years, scientists suggested higher cut-off points of 50 nmol/L or above.[45] These higher cut-off points are based on the effect of serum 25(OH)D levels on PTH secretion, reports on fracture prevention and intestinal calcium absorption rates.[42] However, there is not yet agreement as to the optimal reference ranges that should be used to interpret serum 25(OH)D (Figure 2), and differences in reported prevalence rates for vitamin D deficiency can be expected due to different cut-off points being used.
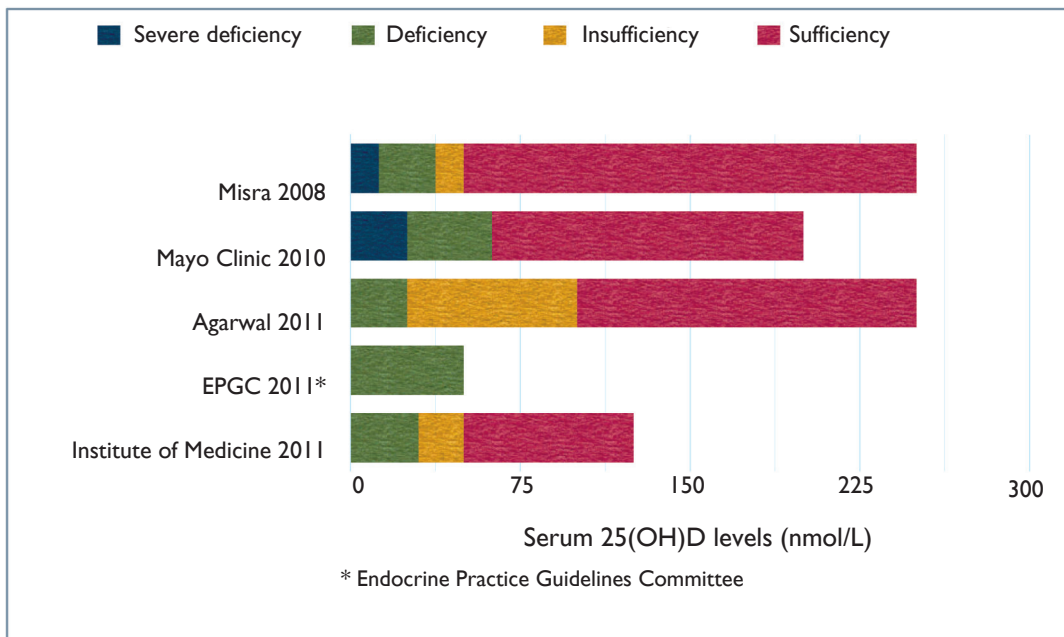

Figure 2: Variation in cut-off points for serum 25(OH)D status in adults[9,16,42,45,46]

IS VITAMIN D DEFICIENCY STILL A PROBLEM TODAY?

Until recently, it was assumed that most people are vitamin D sufficient. However, it seems that there has been a re-emergence of rickets in recent years, even in older children. It is especially dark-skinned infants who are exclusively breastfed beyond three to six months of age, infants whose mothers were vitamin D deficient during pregnancy[16] and premature infants who are most at risk. Also, in countries such as Ethiopia[47] and Tibet,[48] rickets has remained a public health problem. The Centers for Disease Control and Prevention reported a 50% drop in the percentage of vitamin D-sufficient adults in the USA from 1988–1994 to 2001–2004 and that more people are now severely deficient.[49] In a recent report, the global prevalence of hypovitaminosis D varied between 3% and 91%, but the interpretation of the data is hindered by the large variation in cut-off points used for vitamin D deficiency, which ranged from 12,5 nmol/L to 75 nmol/L.[50]

Data on vitamin D status for South Africa is almost non-existing. In vitro studies in Cape Town showed a marked seasonal variation in the production of vitamin D_3, especially during the winter months of April through September. This is in contrast to Johannesburg, where in vitro formation changed little throughout the year.[33] The first data on the vitamin D status of a cohort of healthy 10-year-old children from Johannesburg were published in 2010. The prevalence of vitamin D deficiency was 7% and insufficiency was 19%.[51] A study on 81 adolescents with alcohol use disorder and 81 matched light/non-drinking adolescents in Cape Town showed that vitamin D deficiency was present in 39% of the heavy-drinking and 34% of the light/non-drinking adolescents (unpublished data).[52] A study investigating the vitamin D status of mothers and their children from birth to three years of age in the Breede Valley, Worcester, is currently underway as part of the Community Nutrition Security Project (CNSP) of the HOPE Project of Stellenbosch University. This study will provide some insights into the vitamin D status of mothers and young children.

The reasons for the increased prevalence of vitamin D deficiency globally are not clear, but most likely include a combination of one or more of the following factors:
1) the increase in the cut-off points used for the diagnosis of vitamin D deficiency,
2) more time spent indoors,
3) the use of sunscreen for cancer prevention when going outdoors,
4) the global increase in the prevalence of obesity and
5) increased air pollution in industrial areas.

WHAT ABOUT VITAMIN D TOXICITY?

Vitamin D used to be considered one of the potentially more dangerous vitamins that can lead to toxicity. Contrary to common belief, acute vitamin D overdose is usually the result of industrial accidents, and it has been suggested that vitamin D toxicity is unlikely to occur at intakes below 10 000 IU/day.[53] The long-term effects of chronic exposure to medium to high doses of vitamin D have however not been sufficiently studied.

It is known that vitamin D can cause hypercalcaemia in patients with parathyroid disease, granulomatous disease, sarcoidosis, lymphoma and kidney disease.[40] The Cohort Consortium Vitamin D Pooling Project of Rarer Cancers recently reported an increased risk of pancreatic cancer at serum 25(OH)D > 100 nmol/L.[54] In an ancillary randomised controlled substudy nested within the Women's Health Initiative trial, coronary artery calcified plaque burden was not affected by moderate doses of calcium plus 400 IU vitamin D3.[55] However, a direct relationship between serum 25(OH)D and the quantity of calcified atherosclerotic plaque in African-Americans was reported.[56] The results of this study suggest that there are ethnical differences in the optimal range for serum 25(OH) and that there may be biologically mediated ethnic differences in the regulation of bone and vascular health. Long-term safety studies on the effect of vitamin D supplementation are required regarding the effect on atherosclerosis in African-Americans with vitamin D deficiency. Lastly, in the Women's Health Initiative, the use of both calcium (1 000 mg/day) and vitamin D (400 IU) supplements was associated with a 17% increase in the risk of kidney stones over a period of seven years.[57] The Food and Nutrition Board's recommendation[58] that serum 25(OH)D levels > 125–150 nmol/L be avoided therefore needs to be verified by further studies.

EVIDENCE OF THE BENEFICIAL EFFECT OF VITAMIN D SUPPLEMENTATION

The best-known effect of vitamin D deficiency is a derangement in calcium, phosphorous and bone metabolism. However, abnormalities in VDR activation and function are expected to have adverse effects on cellular function in several biological systems, including those not involved in mineral homeostasis.[59] An association between vitamin D deficiency and many medical conditions was suggested by observational studies. Systematic

reviews, for example, reported inverse relationships between serum 25(OH)D and colorectal adenoma incidence and recurrent adenomas,[60] prostate cancer progression[61] and risk of breast cancer.[62] The prospective study of the National Cancer Institute, on the other hand, did not find an association between serum 25(OH)D and total cancer mortality (with the exception of colorectal cancer mortality),[63] and there was also no evidence of benefit from higher serum 25(OH)D (> 75 nmol/L) or increased risk at lower levels in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers.[54] A systematic review of 13 observational studies showed that the association between vitamin D status and cardiovascular outcomes is uncertain.[64] Other systematic reviews showed that children who received vitamin D supplementation in early childhood had a significantly lower risk of developing type 1 diabetes,[65] and that there is an inverse relationship between serum 25(OH)D and the risk of active tuberculosis[66] and HIV infection.[67]

The evidence from RCTs is summarised in Table 4. Several systematic reviews of RCTs failed to confirm the beneficial effect of vitamin D supplementation in patients suffering from cancer and cardiovascular disease. For falls and fractures, the results from systematic reviews are promising, yet inconsistent. In the case of diabetes, tuberculosis and influenza, no systematic reviews could be identified and the results from single RCTs are inconsistent. For most other conditions that have been linked to vitamin D, no RCTs could be identified. The differences in the results from RCTs may be explained in part by the large degree of heterogeneity in design between individual studies, especially in terms of

- dosage of vitamin D used (varied between 200 IU and 10 000 IU per day);
- duration of follow-up (varied between one month and eight years);
- addition of calcium or not; and
- failure to differentiate between vitamin D sufficiency and deficiency when analysing the results.

The alternate hypothesis, that low levels of vitamin D may be the result of disease rather than its cause, is only now beginning to receive more attention as the results from RCTs are coming to the fore. In one study, for example, vitamin D deficiency developed in patients with peripheral arterial disease as a result of immobility and lack of exposure to sunlight.[68] Even though it is possible that vitamin D deficiency may be the result of disease rather than its cause, its consequences need to be investigated, specifically whether vitamin D supplementation will be beneficial or cause more harm.

A systematic review of 18 RCTs (57 311 participants) showed that daily vitamin D supplementation with 300–2 000 IU was associated with a significant decrease in all-cause mortality rates compared to controls.[69] Evidence of the beneficial effects of vitamin D in individual 'non-classical' medical conditions is however still unconvincing (Table 4).

Table 4: Evidence of the beneficial role of vitamin D supplementation in selected 'non-classical' conditions

Condition	Biological plausibility	Evidence from vitamin D intervention from RCTs
Falls	Muscle tissue expresses VDR[70] that may promote synthesis of new muscle protein, therefore preventing falls.	*Systematic reviews* • 5 RCTs, 400–800 IU D3/active analogue, 800–1 200 mg calcium, 2 months – 3 years follow-up, elderly[71] Significantly reduced falling by 22% • 8 RCTs and 1 prospective risk factor study, 300–800 IU vitamin D3, 18 weeks – 5 years follow-up, vitamin D insufficient postmenopausal women[72] No significant effect on falls • 13 RCTs, vitamin D3, elderly[73] No significant change in group overall Significantly reduced number of falls in trials recruiting participants with lower vitamin D levels (only 260 participants) Adverse effects (hypercalcaemia, renal disease, gastrointestinal effects) reported in three trials • 8 RCTs, 200–1 000 IU vitamin D2 and D3/active analogue, 800–1 200 mg calcium, 2–36 months follow-up, elderly[74] No significant effect at < 700 IU vitamin D Significant reduction in fall risk by 19% on 700–1 000 IU Serum 25(OH)D concentrations of 60 nmol/l or more resulted in a 23% fall reduction. However, the review was heavily criticised and when reanalysed the dose-response relationship disappeared.[64]

	Biological plausibility	Evidence from vitamin D intervention from RCTs
Fractures	Decrease in serum calcium due to vitamin D deficiency will cause secondary hyper-parathyroidism, increased bone resorption, decreased bone mineral density and increased risk of fractures.[75]	*Systematic reviews* • **6 and 8 RCTs, postmenopausal women**[76] No significant effect on non-vertebral fractures Significant reduction in vertebral fractures • **5 RCTs, 400–800 IU vitamin D3, 500–1 200 calcium, 2–5 years follow-up, elderly**[77] 400 IU not effective 700–800 IU/d reduced risk of hip fracture significantly by 26% • **7 RCTs, 400–800 IU vitamin D3, 2–5 years follow-up, elderly**[77] 700–800 IU/d reduced risk of non-vertebral fracture significantly by 23% (no significant benefit with 400 IU/d vitamin D) • **8 and 12 RCTs, 400–770 IU vitamin D3, 500–1 200 mg calcium, 1–7 years follow-up, elderly**[78] No significant effect on hip fractures Significant at the higher dose Significant reduction in non-vertebral fractures, at least 20% if > 400 IU/d vitamin D • **8 RCTs and 1 prospective risk factor study, 300–800 IU vitamin D3, 18 weeks – 5 years follow-up, vitamin D insufficient postmenopausal women**[72] No significant effect on fractures • **7 RCTs, 400–800 IU vitamin D2/D3, 0–1 000 mg calcium, 18–85 months + follow-up**[79] Vitamin D alone not effective Vitamin D with calcium reduced overall risk of hip and overall fracture significantly
Muscle strength	See falls	*Systematic reviews* • **16 RCTs, 400–3 700 IU vitamin D2/9 000 IU D3, 500–1 000 mg calcium, 2–6 months follow-up, adults > 50 years**[80] In only 7 RCTs, a beneficial effect was documented for muscle strength of the lower legs, body sway, physical performance (no meta-analysis) • **17 RCTs, vitamin D, adults**[81] No effect on grip strength, proximal lower limb strength, if serum 25(OH)D > 25 nmol/L Large effect on hip muscle strength in 2 studies where serum 25(OH)D < 25 nmol/L
Cancer	Acts via the autocrine pathway, the immune system and epithelial cell types in the breast, colon, lung, skin and prostate,[9] where 1a-hydroxylases convert 25(OH)D to 1,25(OH)2D intracellularly. The 1,25(OH)2D is involved in inhibition of cell proliferation and cell adhesion, induction of apoptosis, G1 phase cell-cycle arrest, and promotion of cell differentiation, inhibition of angiogenesis, alteration of growth factors and inhibition of metastasis.[82]	*Systematic reviews* • **2 RCTs, 830–1 000 IU/d vitamin D3, 1 400–1 500 mg calcium, 4–5 years follow-up, postmenopausal women, elderly**[83] No significant effect on cancer risk or cancer mortality *Single RCTs* • **400 IU vitamin D, 1 000 mg calcium, 8 years follow-up, postmenopausal women (The Women's Health Initiative)** No significant effect on the risk of colorectal cancer[84] No effect on the risk of breast cancer[85]

	Biological plausibility	**Evidence from vitamin D intervention from RCTs**
Cardio-vascular	Acts via the VDR, which is expressed in vascular smooth muscle cells, renal juxtaglomerular cells and cardiac myocytes. Vitamin D deficiency may be associated with alterations in the structural components of cardiac myocytes and/or the neurohormonal cascade as well as altered cardiac contractility. It is hypothesised that injured myocardium contains ineffective 1-α-hydroxylase activity, resulting in sub-optimal levels of 1,25(OH)2D.[45]	*Systematic reviews* • **11 RCTs, vitamin D2/D3/active analogue, adults** [86] No significant reduction in systolic BP Small significant reduction in diastolic BP • **8 RCTs, 1 000 IU vitamin D, calcium, adults**[87] No significant effect on cardiovascular risk • **10 RCTs, 1 000 IU vitamin D, calcium, healthy adults**[64] No significant effect on BP
Diabetes	Acts via VDRs in pancreatic β-cells, may augment insulin secretion and insulin sensitivity.[5]	*No systematic reviews were identified* *Single RCTs* • **300 000 IU vitamin D3 at baseline, 4 weeks follow-up, type 2 diabetes mellitus (adults)**[88] No improvement in glucose tolerance, insulin secretion or insulin sensitivity • **500 IU vitamin D, 150–250 mg calcium, 12 weeks follow-up, type 2 diabetes mellitus (adults)**[89] Significant improvement of insulin secretion and insulin sensitivity as well as decreased waist circumference and BMI • **2 000 IU vitamin D, 16 weeks follow-up, type 2 diabetes mellitus (adults)**[90] Significant improvement in pancreatic β-cell function • **4 000 IU vitamin D3, 6 months follow-up, type 2 diabetes mellitus (adults)**[91] Significant improvements in insulin sensitivity and insulin resistance in subjects who were insulin resistant with serum 25(OH)D < 50 nmol/l; insulin resistance most improved with serum 25(OH)D > 80 nmol/l Significant reduction in fasting insulin No effect on C-peptide, lipid profile, high-sensitivity C-reactive protein; optimal serum 25(OH)D to reduce insulin resistance was 80–119 nmol/l
Influenza	May be related to seasonal oscillation of serum vitamin D concentrations and effect on innate immunity.[96]	*No systematic reviews were identified* *Single RCTs* • **1 200 IU vitamin D, 4 months follow-up, children**[95] Influenza occurred significantly less often in the vitamin D than in the placebo group between days 31 and 60 only • **2 000 IU vitamin D3, 12 weeks follow-up, adults**[97] No benefit
Tuber-culosis	**Biological plausibility** Increased cellular immunity by acting as an intermediate in the production of antimicrobial peptides such as cathelicidin by monocyte-macrophages,[9] which allow the immune system to recognise and respond to microbes,[92] including mycobacterium tuberculosis.[93]	**Evidence from vitamin D intervention from RCTs** *No systematic reviews were identified* *Single RCTs* • **100 000 IU vitamin D3 at inclusion, 5 and 8 months, 1 year follow-up, tuberculosis patients**[94] Vitamin D does not improve clinical outcome among patients with TB and the trial showed no overall effect on mortality in patients with TB • **Four doses of 2–5 mg vitamin D3, 42 days follow-up, pulmonary tuberculosis patients**[95] No effect on sputum conversion in the group as a whole Significantly expedited sputum culture conversion in participants with the tt genotype of the TaqI vitamin D receptor polymorphism

PREVENTION OF VITAMIN D DEFICIENCY

In November 2010, the Institute of Medicine (IOM) revised the recommendations for daily intake of vitamin D (Table 5),[45] pointing out that these are the levels of intake recommended in the absence of adequate exposure to sunlight. The IOM warns that very high levels of vitamin D (more than 10 000 IUs per day) may cause kidney and tissue damage, challenging the concept that 'more is better'.

The IOM recommendations have been criticised as being overly cautious and in 2011 the Endocrine Practice Guidelines Committee released a new set of even higher recommendations (Table 5),[42] based on the observation that it requires at least 1 000 IU/d of vitamin D to raise the blood levels of 25(OH)D consistently above 75 nmol/L (the proposed cut-off point for sufficiency). In adults and in pregnant women, this amount will be 1 500–2 000 IU/d of vitamin D. Furthermore, it is suggested that obese children and adults and those individuals treated with anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole, and antiretroviral drugs will require at least two to three times the amount of vitamin D recommended for their respective age group. The Committee acknowledged that these recommendations are often based on lower-quality evidence (expert opinion, consensus, inference from basic science experiments and observational studies) and advises that the guidelines be seen as suggestions rather than recommendations. The Committee's guideline for an UL of up to 10 000 IU in adults is based on the results of a dose-ranging study in men, where 10 000 IU/d of vitamin D did not change urinary calcium excretion or serum calcium over a period of five months.[98] It is recommended that blood and urinary calcium levels be monitored in patients who have chronic granuloma-forming disorders (sarcoidosis, tuberculosis) and chronic fungal infections and patients with lymphoma who have activated macrophages that produce 1,25(OH)2D in an unregulated fashion. These patients can have increased calcium absorption from the gut and mobilisation from bone.

Table 5: *Recommended daily vitamin D intakes*

Life stage group	Institute of Medicine[45]				Endocrine Practice Guidelines Committee[42]	
	AI	EAR	RDA	UL[a]	Daily requirement	UL[a]
0–6 months	400 IU			1 000 IU	400–1 000 IU	2 000 IU
6–12 months	400 IU			1 500 IU	400–1 000 IU	2 000 IU
1–3 years		400 IU	600 IU	2 500 IU	600–1 000 IU	4 000 IU
4–8 years		400 IU	600 IU	3 000 IU	600–1 000 IU	4 000 IU
9–13 years		400 IU	600 IU	4 000 IU	600–1 000 IU	4 000 IU
14–18 years		400 IU	600 IU	4 000 IU	600–1 000 IU	4 000 IU
19–70 years		400 IU	600 IU	4 000 IU	1 500–2 000 IU	10 000 IU
>70 years		400 IU	800 IU	4 000 IU	1 500–2 000 IU	10 000 IU
14–18 years pregnancy		400 IU	600 IU	4 000 IU	600–1 000 IU	4 000 IU
19–50 years pregnancy		400 IU	600 IU	4 000 IU	1 500–2 000 IU	10 000 IU
14–18 years lactation		400 IU	600 IU	4 000 IU	600–1 000 IU[b]	4 000 IU
19–50 years lactation		400 IU	600 IU	4 000 IU	1 500–2 000 IU[b]	10 000 IU

AI: Adequate intake; EAR: estimated average requirement; RDA: Recommended dietary allowance; UL: tolerable upper intake level

[a] Upper limit should not be exceeded without medical supervision.

[b] Mother's requirement, 4 000–6 000 IU/d (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

The American Academy of Pediatrics[99] provided the following supplementation guidelines for the prevention of vitamin D deficiency in infants and children:

- All breastfed infants as well as non-breastfed infants and children ingesting less than 1 L of vitamin D-fortified milk per day (400 IU of vitamin D within days of birth). This should continue throughout childhood.

- Infants and children who are already vitamin D insufficient or deficient (1 000 IU/day of vitamin D for infants < 1 month old, 1 000 to 5 000 IU/day for children 1–12 months old and > 5 000 IU/day for children > 12 months old). This should be followed by 400 IU per day of vitamin D supplementation to maintain serum 25(OH)D >50 nmol/L.

- Simultaneous calcium supplementation to prevent hypocalcaemia secondary to decreased demineralisation of bone or increased remineralisation.

In general, a healthful approach to prevent vitamin D deficiency may include the following:

- Light to moderate sun exposure in line with cancer-prevention guidelines

- Adequate intake of good food sources of vitamin D, aiming for the recommended intakes in all groups

- Supplementation of vitamin D in safe amounts in individuals identified as being deficient, insufficient or at risk of deficiency. Currently there is no convincing evidence that supplementation beyond recommended intake is needed for non-calcaemic benefits.

- If high-dose supplementation is required, caution should be exercised and serum levels of 25(OH)D should be monitored to ensure safety

THE WAY FORWARD

In South Africa there is no national data on the vitamin D status of the population, and research on particularly the groups at risk of vitamin D deficiency should be a priority. Ideally, this should form part of the research agenda of the South African National Health and Nutrition Examination Survey, but due to the geographic differences between the provinces, this research could also be undertaken at provincial level in areas where cutaneous synthesis via UVB radiation is expected to be low, such as in the Western Cape. Such data would be required for the development of policy regarding the need for vitamin D supplementation in at-risk groups, including exclusively breastfed infants.

Although food fortification can reach a much larger target group of the population than supplementation, mandatory food fortification with vitamin D cannot be justified for South Africa at this point in time. It is vitally

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